Infeção em Cuidados Intensivos: Epidemiologia, Prognóstico e Biomarcadores

JOANA PEDRO DA SILVA SILVESTRE

Tese para obtenção do grau de Doutor em Medicina

na Especialidade em Medicina Interna

na NOVA Medical School | Faculdade de Ciências Médicas

Setembro, 2018

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Agradecimentos

" Not everything that counts can be counted. And not everything that can be counted counts"

ALBERT EINSTEIN

O longo percurso que levou à origem deste trabalho, obrigou o envolvimento colectivo de muitas pessoas, às quais, algumas, não podendo deixar de aqui mencionar algumas palavras.

Em primeiro lugar, queria agradecer ao Professor Doutor Pedro Póvoa que desde cedo me despertou uma visão diferente do conhecimento médico, e me tem demonstrado que os limites somos nós que os traçamos. Para além de orientador envidando todos os esforços para resolver os mais diversos problemas associados ao meu projeto, tem sido um elemento motivador não me fazendo desistir nos momentos de maior dificuldade quer a nível profissional quer a nível pessoal.

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Em terceiro lugar, à minha família ao Baltazar pela sua infinita paciência e ao Tiago e á Maria por colocarem prioridades na minha vida, sendo eles a primeira, mas não a única.

Por último, a toda a equipa da Unidade de Cuidados Intensivos Polivalente do Hospital São Francisco Xavier e ao Serviço de Cirurgia do Hospital de São Francisco Xavier, em especial ao Dr. Jorge Rebanda pela parceria e cooperação. Sem eles não teria sido possível.

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APACHE - Acute Physiology and Chronic Health Evaluation

DA – deiscência anastemótica

FI – Fator de impacto

FiO_2 - fração inspirada de oxigénio

Gradiente A-a - gradiente Alvéolo-arterial

IF – Impact factor

IL1 – interteucina 1

IL6 – interleucina 6

MeSH – termo de assunto médico

MODS - Multiple Organ Dysfunction Score

MPM - Mortality Probability Mode

PCR – proteína C-reactiva

PCT – procalcitonina

pH – potencial de hidrogénio

SAPS - Simplified Acute Physiology Score

SIRS – Síndrome de resposta inflamatória sistémica

SOFA - Sequential Organ Failure Assessment

suPAR - receptor solúvel do ativador de plasminogénio tipo uroquinase

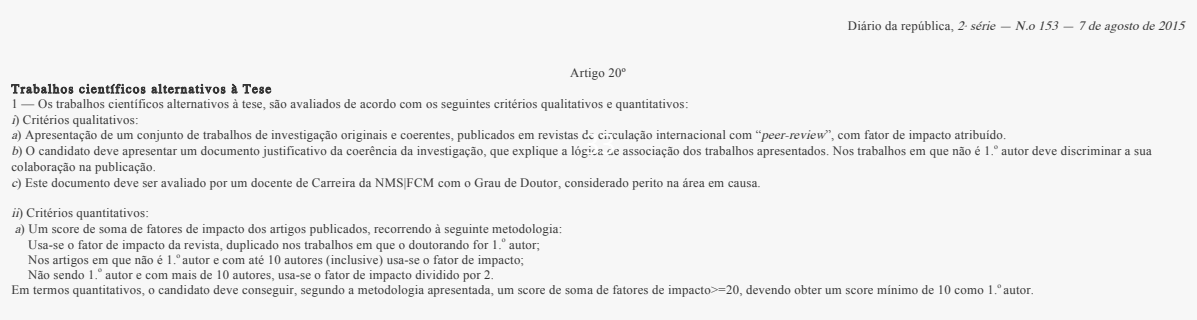
UCI - unidade de Cuidados Intensivos

uPA - ativador do plasminogénio tipo uroquinase

uPAR – receptor do ativador do plasminogénio tipo uroquinase

1 Resumo

Esta tese de doutoramento é apresentada de acordo com o regulamento vigente do ciclo de estudos conducente ao grau de Doutor em Medicina da NOVA Medical School|Faculdade de Ciências Médicas da Universidade Nova de Lisboa, número 519/2015 publicado em Diário da República, 2ª série, Nº 153, a 7 de agosto de 2015. A tese é apresentada de acordo com o Artigo 20º com trabalhos científicos alternativos à Tese.



Diário da república, *2.ª série — N.o 153 — 7 de agosto de 2015*

Artigo 20º

Trabalhos científicos alternativos à Tese

1 — Os trabalhos científicos alternativos à tese, são avaliados de acordo com os seguintes critérios qualitativos e quantitativos:

i) Critérios qualitativos:

a) Apresentação de um conjunto de trabalhos de investigação originais e coerentes, publicados em revistas de circulação internacional com "*peer-review*", com fator de impacto atribuído.

b) O candidato deve apresentar um documento justificativo da coerência da investigação, que explique a lógica de associação dos trabalhos apresentados. Nos trabalhos em que não é 1.º autor deve discriminar a sua colaboração na publicação.

c) Este documento deve ser avaliado por um docente de Carreira da NMS|FCM com o Grau de Doutor, considerado perito na área em causa.

ii) Critérios quantitativos:

a) Um score de soma de fatores de impacto dos artigos publicados, recorrendo à seguinte metodologia:

Usa-se o fator de impacto da revista, duplicado nos trabalhos em que o doutorando for 1.º autor;

Nos artigos em que não é 1.º autor e com até 10 autores (inclusive) usa-se o fator de impacto;

Não sendo 1.º autor e com mais de 10 autores, usa-se o fator de impacto dividido por 2.

Em termos quantitativos, o candidato deve conseguir, segundo a metodologia apresentada, um score de soma de fatores de impacto>=20, devendo obter um score mínimo de 10 como 1.º autor.

Os trabalhos científicos propostos, em ordem cronológica, são:

- **Artigo 1 :** Silvestre J, Póvoa P, Coelho L, Almeida E, Moreira P, Fernandes A, Mealha R, Sabino H. **Is C-reactive protein a good prognostic marker in septic patients?** Intensive Care Med. 2009 May;35(5):909-13.

  Fator de impacto 15.008

- **Artigo 2:** Silvestre J, Coelho L, Póvoa P. **Should C-reactive protein concentration at ICU discharge be used as a prognostic marker?** BMC Anesthesiol. 2010 Sep 27; 10:17.

  Fator de impacto 1.701

- **Artigo 3:** Silvestre JP, Coelho LM, Póvoa PM. **Impact of fulminant hepatic failure in C-reactive protein?** J Crit Care. 2010 Dec;25(4):657.e7-12.

  Fator de impacto 2.191.

- **Artigo 4:** Araújo I, Gonçalves-Pereira J, Teixeira S, Nazareth R, Silvestre J, Mendes V, Tapadinhas C, Póvoa P. **Assessment of risk factors for in-hospital mortality after intensive care unit discharge.** Biomarkers. 2012 Mar;17(2):180-5.

  Fator de impacto 2,226.

- **Artigo 5:** Silvestre J, Rebanda J, Lourenço C, Póvoa P. **Diagnostic accuracy of C-reactive protein and procalcitonin in the early detection of infection after elective colorectal surgery - a pilot study.** BMC Infect Dis. 2014 Aug 16;14:444.
  Fator de impacto 2.949.
- **Artigo 6:** Silvestre J, Coelho L, Gonçalves-Pereira J, Mendes V, Tapadinhas C, Póvoa P. **suPAR in the assessment of post-ICU prognosis - pilot study**. Artigo aceite na Revista Brasileira de Terapia Intensiva.
  Fator de impacto 0.47.

De acordo com os critérios quantitativos, o total da soma dos artigos publicados recorrendo à metodologia citada no artigo 20º tem o somatório de 46,864 (Tabela 1).

Tabela 1: Somatório do fator de impacto dos artigos publicados

Revista	Fator de impacto (FI)	Fator de ponderação	Score calculado
Intensive Care Medicine	15.008	2 x FI	30.016
BMC Anestesiology	1.701	2 x FI	3.402
Journal of Critical Care	2.191	2 x FI	4.382
Biomarkers	2.226	1 x FI	2.226
BMC Infectious Diseases	2.949	2 x FI	5.898
Revista Brasileira de Terapia Intensiva	0,47	2 x FI	0.94
Score total			**46.864**

O objectivo desta tese de doutoramento foi estudar o papel dos biomarcadores como marcadores de prognóstico no doente critico. Em simultâneo foi efetuado um estudo preliminar sobre o papel dos biomarcadores como marcadores de infeção no pós-operatório eletivo.

2 Abstract

This doctoral thesis is presented in accordance with the current regulation of the cycle of studies leading to the Doctorate degree of NOVA Medical School of the Universidade Nova de Lisboa number 519/2015 published in Diário da República, 2nd series, N°. 153, August 7. The thesis is presented in accordance with article number 20 with scientific published articles.

Diário da república, 2.a série — N.o 153 — 7 de agosto de 2015

Article 20

Scientific works alternative to Thesis
1 - The scientific works alternative to the thesis are evaluated according to the following qualitative and quantitative criteria:
(i) Qualitative criteria:
a) Presentation of a set of original and coherent research papers, published in journals of international circulation with peer-review, with attributed impact factor.
b) The candidate must present a document justifying the coherence of the research, in witch is explained which explains the consistency and the alignment of the papers presented. In works in which it is not 1.st the author must discriminate his collaboration in the publication.
c) This document must be evaluated by a NMS | FCM Professor Career with the Degree of Doctor, considered expert in the area in question.

(ii) Quantitative criteria:
A sum of a score based on the impact of published articles, using the following methodology:
The l impact factor of the journal is duplicated in the paper in which the doctorate is 1st author;
In articles in which the author is not 1st author and with more than to 10 authors (inclusive) the impact factor is used;
Not being 1st author and with more than 10 authors, the impact factor is divided by 2 is used.
In quantitative terms, the candidate must achieve, according to the presented methodology, a score of sum of factors of impact> = 20, obtaining a minimum score of 10 as 1st author.

In chronologic order, the scientific articles proposed are:

- **Article 1:** Silvestre J, Póvoa P, Coelho L, Almeida E, Moreira P, Fernandes A, Mealha R, Sabino H. **Is C-reactive protein a good prognostic marker in septic patients?** Intensive Care Med. 2009 May;35(5):909-13.
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- **Article 2:** Silvestre J, Coelho L, Póvoa P. **Should C-reactive protein concentration at ICU discharge be used as a prognostic marker?** BMC Anesthesiol. 2010 Sep 27; 10:17.
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- **Article 3:** Silvestre JP, Coelho LM, Póvoa PM. **Impact of fulminant hepatic failure in C-reactive protein?** J Crit Care. 2010 Dec;25(4):657.e7-12.
  Impact factor 2.191.
- **Article 4:** Araújo I, Gonçalves-Pereira J, Teixeira S, Nazareth R, Silvestre J, Mendes V, Tapadinhas C, Póvoa P. **Assessment of risk factors for in-hospital mortality after intensive care unit discharge.** Biomarkers. 2012 Mar;17(2):180-5.
  Impact factor 2.154

- **Article 5:** Silvestre J, Rebanda J, Lourenço C, Póvoa P. **Diagnostic accuracy of C-reactive protein and procalcitonin in the early detection of infection after elective colorectal surgery - a pilot study.** BMC Infect Dis. 2014 Aug 16;14:444.
  Impact factor 2.949.
- **Article 6:** Silvestre J, Coelho L, Gonçalves-Pereira J, Mendes V, Tapadinhas C, Póvoa P. **suPAR in the assessment of post-ICU prognosis - pilot study**. Accepted for publication in the Revista Brasileira de Terapia Intensiva.
  Impact factor 0.47.

According to the quantitative criteria, the calculated score of the articles using the methodology cited in article 20 has the total score of 46.864 (Table 1).

Table 1: Total score pontuation of impact factor of published articles

Review	Impact Factor (IF)	Weighting factor	Calculated score
Intensive Care Medicine	15.008	2 x FI	30.016
BMC Anestesiology	1.701	2 x FI	3.402
Journal of Critical Care	2.191	2 x FI	4.382
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Revista Brasileira de Terapia Intensiva	0,47	2 x FI	0.94
Total score			**46.864**

The main objective of this doctoral thesis was to study the role of biomarkers as prognostic markers in the critical patient. At the same time, a preliminary study on the role of biomarkers as markers of infection in the elective postoperative period has been made.

3 Introdução

A doença crítica está associada a maior morbi-mortalidade. As alterações na homeostasia do doente resultam do insulto agudo, da capacidade do doente responder a esse insulto e da terapêutica efetuada. Apesar da melhoria dos cuidados prestados nas unidades de cuidados intensivos (UCI), a mortalidade hospitalar dos doentes que sobrevivem aos cuidados intensivos persiste elevada. Tal pode resultar da irreversibilidade da situação clínica, o que constitui uma "morte previsível", mas pode igualmente resultar da persistência da doença aguda ou do seu impacto tardio na situação de saúde do doente. A condição clínica dos doentes tem sido o parâmetro utilizado para determinar a aptidão destes doentes para a alta da UCI e para a alocação destes doentes nos diferentes destinos.

Os índices de gravidade calculados nas primeiras horas de admissão dos doentes na UCI têm-se mostrado pouco sensíveis na predição da mortalidade após a alta da UCI. Alguns autores defendem que um fator de risco potencial na alta hospitalar é o estado pró ou anti-inflamatório do doente. Neste sentido, vários biomarcadores têm sido estudados como marcadores de prognóstico.

Embora o termo biomarcador seja relativamente novo, os biomarcadores têm sido utilizados desde há muito tempo. Um exemplo disso é a temperatura corporal, um biomarcador de febre.

A definição de biomarcador (marcador biológico) foi introduzido em 1989 como termo de assunto médico (MeSH), sendo definido como um parâmetro biológico mensurável e quantificável (por exemplo, concentração específica de uma enzima, concentração específica de uma hormona, distribuição fenotípica específica de um gene numa população, presença de determinada substância biológica) que servia de índice para avaliar situações relacionadas com saúde/doença e a fisiologia.

Em 2001, um grupo de trabalho padronizou a definição de biomarcador como uma característica que é medida e avaliada objetivamente, como um indicador de processos biológicos normais, processos patogénicos ou respostas farmacológicas a uma

intervenção terapêutica, definindo várias categorias de biomarcadores (1).

A utilidade de um biomarcador está na capacidade de fornecer informações para além daquelas prontamente disponíveis a partir dos dados fisiológicos de rotina e da semiologia clínica. Esta informação adicional pode fornecer informações sobre a fisiopatologia ou o prognóstico de um processo de doença assim como ajudar numa decisão terapêutica, além de facilitar a terapêutica de titulação ou monitorizar a resposta à intervenção/terapêutica. A Tabela 2 resume as diferentes categorias dos biomarcadores.

Tabela 2: **Classificação clínica dos diferentes tipos de biomarcadores**

Prognóstico
Identificar doentes com elevado risco de resultado adverso de forma a providenciar uma intervenção profilática ou outro teste diagnóstico.
Diagnóstico
Estabelecer um diagnóstico para determinar uma decisão de tratamento e fazê-lo da maneira mais confiável, mais rápida ou mais económica do que os métodos disponíveis.
Estratificação de risco
Identificar subgrupos de doentes dentro de um determinado grupo de diagnóstico que podem apresentar maior benefício ou prejuízo com a intervenção terapêutica.
Monitorização
Medir a resposta à intervenção, para permitir a titulação da dose ou duração do tratamento.
"Surrogate endpoint"
Fornecer uma medida mais sensível das consequências do tratamento que pode substituir uma medida direta num resultado centrado no paciente

Adaptado de Marshall JC and Reinhart K, Biomarkers of sepsis, Critical Care Medicine 2009, 37, 2290–22 (2)

Um biomarcador pode ser mensurável através de uma amostra biológica (sangue, urina, amostras tecidulares, entre outras), através de exames imagiológicos (ecocardiograma, tomografia) ou de dados fisiológicos (pressão arterial, registo electrocardiográfico).

No âmbito do doente crítico qualquer disfunção orgânica é susceptível de ser avaliada com maior ou menor acurácia com recurso a um marcador biológico seja ele de diagnóstico, prognóstico ou de resposta. Contudo, os valores numéricos obtidos nestes biomarcadores nunca deverão ser usados de forma isolada.

Existem áreas clínicas na Medicina Intensiva em que os biomarcadores têm tido um papel crescente e eficiente na sua utilização, nomeadamente na inflamação e sépsis, na patologia cardiovascular, na disfunção renal, nos distúrbios nutricionais e metabólicos.

Nesta tese analisou-se o comportamento dos biomarcadores no doente critico, Proteína C-reactiva (PCR) e do receptor solúvel do ativador de plasminogénio tipo uroquinase (suPAR), isoladamente ou em associação com os índices de gravidade, como marcadores de prognóstico, quer na mortalidade na UCI quer na mortalidade hospitalar. Foi também analisado o comportamento da PCR no doente com insuficiência hepática aguda.

Em simultâneo, de forma a complementar o comportamento dos biomarcadores na identificação de infeção documentada foi efetuado um estudo prospectivo envolvendo doentes de cirurgia eletiva avaliando o comportamento dos biomarcadores, nomeadamente da PCR e da procalcitonina (PCT) e o seu potencial na deteção de complicações infeciosas pós operatórias cirúrgicas e não cirúrgicas.

4 Biomarcadores no prognóstico do doente critico

A avaliação do prognóstico do tratamento médico foi iniciado por Nightingale em 1863, com a medição da taxa de mortalidade durante um período de 6 meses após a implementação das medidas de saneamento e higienização no hospital militar de Scutari, na Turquia, constatando um descida de 43% para 2%. O foco nos resultados como um método para medir os esforços de qualidade foi uma grande contribuição para a pesquisa na Medicina (3).

Inicialmente, o prognóstico no doente crítico fundamentava-se apenas no julgamento subjetivo dos clínicos. O rápido e crescente desenvolvimento de UCIs criou a necessidade de medidas quantitativas e clinicamente relevantes, a fim de avaliar a eficácia das práticas de tratamento bem como *benchmarking*. Deste modo, foram desenvolvidos nas últimas décadas sistemas de pontuação, os índices de gravidade que permitem uma estimativa da mortalidade intra-hospitalar.

Estes índices são obtidos através da colheita de dados específicos para cada doente (Tabela 3) (4). Uma ponderação é aplicada a cada variável e a soma das pontuações individuais ponderadas produz um índice de gravidade. As escalas de pontuação fisiológica aplicadas nos doentes críticos têm sido defendidas como apresentando várias vantagens em relação aos sistemas baseados em diagnóstico uma vez que podem ser usados em outros grupos de doentes.

Os doentes críticos internados em unidades de cuidados intensivos podem apresentar falência única ou múltipla de órgãos e, portanto, não apresentam um diagnóstico claramente definido. Às vezes, nenhum diagnóstico pode ser feito, quer na admissão ou retrospectivamente. Um sistema de pontuação baseado em diagnósticos será, portanto, inaplicável.

Os índices de gravidade consistem essencialmente em duas partes: uma pontuação de gravidade, que é um número (geralmente quanto maior, mais grave a situação) e uma probabilidade de mortalidade calculada.

Tabela 3: Dados usados na obtenção de índices de gravidade

Comorbilidades
Neoplasias
Técnica de substituição renal
Corticoides/terapêutica imunossupressora (exemplo: radioterapia)
Doença hepática
Doença hematológica
Parâmetros fisiológicos
Cardiovascular: pressão arterial media, frequência cardíaca
Respiratórios: FiO_2, gradiente A-a, frequência respiratória
Temperatura corporal
Escala de coma de Glasgow
Índices bioquímicos e hematológicos
Hemoglobina/hematócrito, leucócitos, coagulação, creatinina, sódio, potássio, pH arterial
Origem da admissão
Médico ou cirúrgico
Urgência ou eletiva
Dados demográficos/clínicos do doente
Idade
Regiões anatómicas/órgão afectados

Adaptado de Bouch DC and Thompson JP, Severity scoring systems in the critically ill, *Continuing Education in Anaesthesia Critical Care & Pain* 2008, 8 (5), 181–185

A maioria dos índices de gravidade é calculada a partir dos dados obtidos nas primeiras 24h de internamento na UCI [por exemplo: o APACHE (*Acute Physiology And Chronic Health Evaluation*), o SAPS (*Simplified Acute Physiology Score*) e o MPM (*Mortality Prediction Mode*)]. Outros índices de gravidade são diários e são obtidos através da

colheita de dados de forma seriada e sequencial durante toda a permanência na UCI [por exemplo: o SOFA (*Sequential Organ Failure Assessment*) e o MODS (*Multiple Organ Dysfunction*)].

Um índice de gravidade ideal teria as seguintes características: variáveis de rotina fáceis de usar, boa calibração, elevado nível de discriminação, aplicabilidade a todas as populações de doentes, podendo ser usado em diferentes países e capaz de prever o estado funcional ou a qualidade de vida após a alta da UCI. Atualmente nenhum índice de gravidade possui todas estas características.

Um fator de risco potencial que tem sido apontado no doente critico à data de alta da UCI é a persistência do estado pró ou anti-inflamatório do doente (5). Nos últimos anos, o termo inflamação de baixo grau tem sido amplamente utilizado para descrever um mecanismo subjacente que leva à doença em indivíduos saudáveis (6).

Alguns marcadores têm sido usados na correlação com disfunção orgânica e com mortalidade na UCI, no entanto, os resultados não têm sido consensuais (7, 8).

No âmbito desta tese foram realizados vários estudos para analisar a mortalidade e readmissão hospitalar após a alta da UCI em relação aos sinais de inflamação.

Os biomarcadores analisados nesta tese no âmbito do doente critico foram a proteína C-reactiva e o receptor solúvel do ativador de plasminogénio tipo uroquinase.

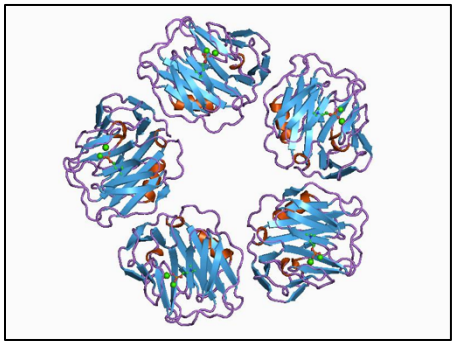
4.1 Proteina C reactiva

A Proteína C-reactiva é o protótipo de proteína de fase aguda, com marcada elevação da concentração em resposta a diversos estímulos inflamatórios. Foi descrita em 1930 por Tillet e Francis no soro de doentes com pneumonia pneumocócica, como uma substância que precipitava com o polissacárido C do *Streptococcus pneumoniae* tendo-a denominado como fracção C (9). Em 1941 foi identificada como uma proteína que era sintetizada não por bactérias, mas pelo organismo como resposta a um insulto inflamatório (10). Quarenta anos após a sua descoberta, Volanakis e Kaplan identificaram o receptor específico para a PCR, como fosfocolina, parte do ácido teicóico da parede

celular do pneumococo (9). Apesar da fosfocolina ter sido o primeiro receptor descrito, é sabido atualmente que a PCR interage com vários estímulos e ativa a via clássica do complemento, estimula a fagocitose e liga-se aos receptores da imunoglobulina (11).

Atualmente sabe-se que pertence a uma família de proteínas denominada de pentraxinas, assim chamadas porque formam um pentâmero cíclico composto por 5 subunidades similares e ligadas de forma não covalente, organizadas numa estrutura discóide muito estável (Figura 1) (12, 13). Esta família de proteínas é muito conservadora na evolução da espécie, sugerindo um papel fisiológico importante. Esta teoria é suportada pelo facto de até à data não serem conhecidas deficiências de PCR em humanos. Tem sido sugerido que a PCR atua como pro-inflamatório ou com capacidade anti-inflamatórias na defesa da respostado hospedeiro (14). No entanto a função precisa das suas propriedades biológicas continua a ser controversa (11).

Figura 1: Estrutura pentamérica da proteína C -reactiva



O gene da PCR está localizado no braço curto do cromossoma 1 e contém apenas um intrão que separa a região que codifica o péptido sinal daquela que codifica a proteína madura. A indução da PCR nos hepatócitos é principalmente regulada ao nível transcripcional pela citoquina interleucina-6 (IL-6), um efeito que pode ser potenciado pela interleucina-1 (IL-1) (15).

A investigação da PCR no doente crítico tem tido várias abordagens nomeadamente como adjuvante no diagnóstico de infeção, como marcador de prognóstico avaliando a sua correlação com a gravidade da doença e por último na resposta à terapêutica permitindo a variação deste marcador ajustar o tempo de antibioterapia.

O estudo do valor prognóstico da PCR tem sido igualmente investigada, com resultados contraditórios (5).

No sentido de apurar o papel dos biomarcadores no prognóstico dos doentes críticos na presença ou na ausência de infeção foram desenvolvidos os trabalhos dos quais resultaram os artigos publicados acima mencionados: **Artigo 1**, **Artigo 2** e **Artigo 4.**

Estes trabalhos avaliam o valor da PCR como marcador de prognóstico quer na UCI (**Artigo 1**) quer em ambiente hospitalar (**Artigo 2 e 4**). Este biomarcador foi usado tanto isoladamente como em associação com os índices de gravidade.

4.1.1 Proteína C-reactiva na insuficiência hepática

A PCR sérica é sintetizada exclusivamente pelos hepatócitos no fígado em resposta às citoquinas pró-inflamatórias. Têm sido descritos locais de sínteses extra-hepática nos neurónios, na placa aterosclerótica, monócitos e linfócitos (16, 17). Os mecanismos que regulam a síntese nestes locais é desconhecido, sendo portanto pouco provável que influenciem os níveis plasmáticos da PCR.

Na população em geral, indivíduos saudáveis tendem a ter concentrações de PCR estáveis para cada indivíduo, exceptuando picos ocasionais presumivelmente relacionados a infeções menores ou subclínicas, inflamação ou trauma. Não há variação sazonal significativa na concentração de PCR sendo o coeficiente de variação das medidas repetidas com intervalos de anos de cerca de 0,5, semelhante ao do colesterol (18).

A PCR tem uma semivida de cerca de 18 horas, começa a ser secretada cerca de 6 horas após o estimulo e o seu ritmo de síntese é diretamente proporcional à intensidade do estimulo (19). Quando o estímulo para o aumento da produção cessa, a concentração de PCR circulante diminui rapidamente. Os valores de PCR não apresentam variação diurna, não são influenciados pela alimentação, e por poucos fármacos (20). Os seus valores também não são alterados pelas técnicas de depuração renal (21). A única exceção a esta cinética deste biomarcador é a insuficiência hepática grave.

A síntese de proteíca, nomeadamente da PCR, parece estar reduzida em pacientes com insuficiência hepática. No entanto, foi demonstrado que doentes com cirrose sem

infeção tinham níveis mais altos de IL-6 e aumentavam a expressão de receptores do fator de necrose tumoral (22, 23). Portanto, avaliar os níveis de PCR que realmente ajudariam a diagnosticar a infeção em doentes com doença hepática avançada ainda é difícil continuando ainda a haver uma escassez de dados.

Neste contexto, foi analisada a cinética deste biomarcador nos doentes com sépsis e falência hepática aguda grave sendo os resultados do estudo apresentados no **Artigo 3**.

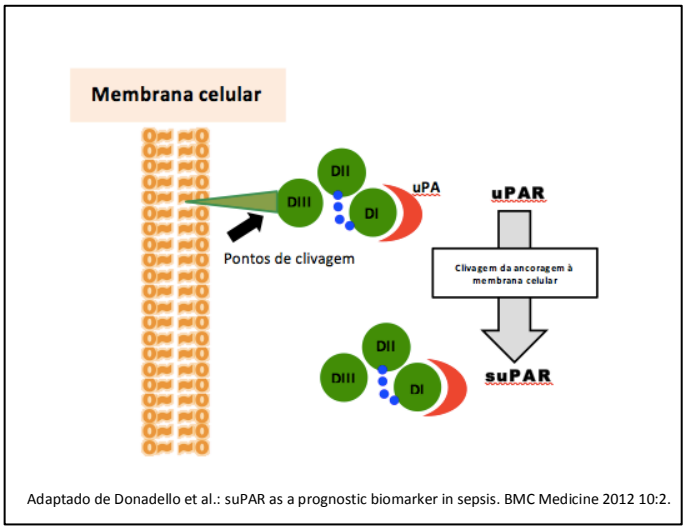
4.2 Receptor solúvel do ativador de plasminogénio tipo uroquinase

O sistema ativador do plasminogênio tipo uroquinase (uPA) consiste numa protease, num receptor (uPAR) e nos seus inibidores.

Em 1990, o uPAR foi clonado e, em 1991, Ploug et al. identificou sua forma solúvel (suPAR) (24, 25). O uPAR é expresso em vários tipos de células, incluindo neutrófilos, linfócitos, monócitos / macrófagos, células endoteliais e tumorais.

Após a clivagem da superfície celular, o suPAR pode ser encontrado no sangue e noutros fluidos orgânicos em todos os indivíduos, existindo em três formas (I-III, II-III e I) que possuem diferentes propriedades relacionadas com as diferenças estruturais (**Figura 1**) (26).

Figura 2: Estrutura esquematizada do uPAR e o mecanismo de formação do suPAR.
DI, DII e DIII representam as três formas homólogas do suPAR.



Adaptado de Donadello et al.: suPAR as a prognostic biomarker in sepsis. BMC Medicine 2012 10:2.

Desde a sua descoberta têm-se realizados múltiplos estudos na investigação do papel do uPAR na carcinogénese, na biologia celular e molecular do uPAR e no papel do suPAR como biomarcador de risco nas doenças infeciosas (26-28).

Nos últimos 20 anos, tem-se demonstrado que o uPAR⁄suPAR participa numa série de funções imunológicas, nomeadamente na adesão celular, migração, quimiotaxia, proteólise, ativação imunológica, remoção de tecidos, invasão e transdução de sinal (29).

Além do seu papel na adesão e migração, o suPAR recentemente demonstrou inibir a remoção das células apoptóticas pelos fagócitos, nomeadamente pelos neutrófilos (30), enquanto a forma ligada à membrana de uPAR demonstrou facilitar a fagocitose de bactérias (31). A clivagem do uPAR pode, portanto, refletir um compromisso funcional da defesa do hospedeiro, em vez de um marcador substituto da inflamação, o que poderia explicar o maior valor prognóstico do suPAR comparado com outros biomarcadores.

Numerosos estudos observacionais demonstraram que os níveis sistémicos de suPAR encontram-se aumentados nos doentes com cancro (32, 33), e em várias doenças infeciosas e inflamatórias (34-41).

No doente crítico os níveis de suPAR também se encontram elevados (42), mas a sua utilidade tem sido questionável. São vários os estudos que demonstram que embora os níveis sistémicos de suPAR estejam elevados nos doentes com sépsis, bacteriémia e síndrome de resposta inflamatória sistémica (SIRS) o seu valor diagnóstico é baixo, sendo este biomarcador um marcador inespecífico de inflamação (43).

Apesar de não se apresentar como um bom biomarcador de infeção, tem-se constatado em alguns estudos que doentes mais graves internados na UCI, que apresentam níveis mais elevados de suPAR, parecem ter um pior *outcome* (43). No entanto o papel deste biomarcador como marcador prognóstico da mortalidade hospitalar após a alta da UCI não foi avaliado. Os níveis sistêmicos de suPAR permanecem elevados por muito tempo após a recuperação clínica e só diminuem após várias semanas (44). Portanto, o uso de suPAR pode ser um biomarcador de prognóstico promissor nos doentes críticos.

Neste sentido, foi estudado a relação do biomarcador com a mortalidade hospitalar dos que tiveram alta da unidade de cuidados intensivos para a enfermaria. Os resultados do estudo são apresentados **Artigo 6.**

5 Biomarcadores na monitorização das complicações pós-cirúrgicas

O papel dos biomarcadores no diagnóstico de infeção tem sido crescente. Mais do que o valor absoluto, a importância da sua cinética tem sido determinante para o diagnóstico e monitorização da infeção.

Póvoa et al demonstrou que a monitorização diária da PCR, assim como a identificação de diferentes padrões de cinética permitiu identificação de doentes que viriam a desenvolver infeção e sépsis (45). Mais recentemente, a cinética dos biomarcadores (PCR e PCT) demonstrou utilidade no diagnóstico de pneumonias associada à ventilação mecânica (46).

De forma a complementar o comportamento dos biomarcadores na identificação de infeção documentada foi efetuado um estudo prospectivo, envolvendo doentes de cirurgia eletiva e avaliado o comportamento dos biomarcadores na distinção de doentes infectados versus não infectados.

Cerca de 30% da patologia dos doentes internados é do foro cirúrgico (47). A cirurgia eletiva constitui um dos motivos de admissão na UCI com taxas médias de ocupação por complicação pós-cirúrgica que variam entre 15-17% (48).

A recuperação pós cirúrgica dos doentes com doença colorretal melhorou com os avanços das técnicas cirúrgicas e com a instituição de protocolos de recuperação padronizados (49).

A deiscência anastomótica (DA) continua a ser uma das complicações mais temidas após a cirurgia colorretal, com taxas de 3-27% dependendo de fatores de risco específicos (50-52). Embora um conjunto de fatores de risco tenha sido relatado, a DA permanece difícil de prevenir e diagnosticar precocemente. Em muitos doentes, o curso é insidioso com sintomas inespecíficos sendo o diagnóstico tardio (53, 54).

No pós-operatório imediato, a sépsis intra-abdominal pode ser difícil de distinguir do SIRS secundário à cirurgia. A sépsis é a complicação major dos doentes cirúrgicos internados na UCI com elevada morbimortalidade (55).

Neste contexto, foi efetuado um estudo prospectivo em parceria conjunta com o Serviço de Cirurgia do Hospital São Francisco Xavier/Centro Hospitalar de Lisboa Ocidental onde foram estudados os doentes submetidos a colectomia eletiva com anastomose colorrectal. Foi efetuado o seguimento dos doentes desde o momento prévio à cirurgia até ao 12º dia de pós-operatório ou alta. Foram medidos diariamente os biomarcadores (PCT e PCR) e efetuada a análise comparativa entre os doentes que desenvolveram e os que não desenvolveram infeção. Os resultados do estudo são apresentado no **Artigo 5**.

6 Publicações

Seguem-se os trabalhos científicos publicados propostos alternativos à tese (Artigo 20º , número 519/2015 publicado em Diário da República, 2ª série, Nº 153, a 7 de agosto de 2015).

6.1 Artigo 1: Is C-reactive protein a good prognostic marker in septic patients?

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BRIEF REPORT

Is C-reactive protein a good prognostic marker in septic patients?

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Abstract *Rationale:* Several studies have shown that C-reactive protein (CRP) is a marker of infection. The aim of this study was to evaluate CRP as marker of prognosis outcome in septic patients and to assess the correlation of CRP with severity of sepsis. *Methods:* During a 14-month period, we prospectively included all patients with sepsis admitted to an intensive care unit (ICU). Patients were categorized into sepsis, severe sepsis and septic shock. Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment (SOFA) score, CRP, body temperature and white cell count (WCC) of the day of sepsis diagnosis were collected. *Results:* One hundred and fifty-eight consecutive septic patients (mean age 59 years, 98 men, ICU mortality 34%) were studied. The area under the receiver operating characteristics curves of APACHE II, SAPS II, SOFA, CRP, body temperature and WCC as prognostic markers of sepsis were 0.75 [95% confidence interval (CI) 0.67–0.83], 0.82 (95% CI 0.75–0.89), 0.8 (95% CI 0.72–0.88), 0.55 (95% CI 0.45–0.65), 0.48 (95% CI 0.38–0.58) and 0.46 (95% CI 0.35–0.56), respectively. In the subgroup of patients with documented sepsis we obtained similar results. The ICU mortality rate of septic patients with CRP < 10, 10–20, 20–30, 30–40 and >40 mg/dL was 20, 34, 30.8, 42.3 and 39.1%, respectively ($P = 0.7$). No correlation was found between CRP concentrations and severity of sepsis. *Conclusions:* In septic patients, CRP of the day of sepsis diagnosis is not a good marker of prognosis.

Keywords C-reactive protein · Sepsis · Infection · Organ failure · Prognosis

Introduction

Sepsis is a clinical syndrome that results from the interaction between the infecting microorganism and the host immune, inflammatory and coagulation responses [1]. Measurement of circulating concentrations of biomarkers may prove to be useful in the stratification of sepsis and hypothetically could be used to decide the administration of sepsis specific therapies [2].

Amongst biomarkers, C-reactive protein (CRP) and procalcitonin (PCT), proved to be useful in the infection diagnosis, infection prediction and monitoring response to antibiotics [3, 4]. Besides, the ability of biomarkers to assess sepsis prognosis has also been studied [3–5].

Despite the recent findings, the evaluation of prognosis in septic patients still depends on the assessment of physiological variables and presence of comorbidities [5–8].

The aim of our study was to investigate whether CRP could be used as prognostic marker in septic patients as well as in the subgroup with documented sepsis. Additionally, we evaluated the correlation between CRP concentrations and severity of sepsis.

Patients and methods

A single centre prospective observational cohort study was conducted during a 14-month period (November 2001–December 2002) in the intensive care unit (ICU) of Garcia de Orta Hospital.

Patients were included if they fulfilled criteria for sepsis. Sepsis was considered according to the Centers for Disease Control and Prevention definitions [9]. If the patient presented more than one septic episode only the first was considered.

Severity of illness was assessed by calculating Acute Physiologic and Chronic Health Evaluation (APACHE) II score [10], Simplified Acute Physiology Score (SAPS) II [11] and Sequential Organ Failure Assessment (SOFA) scores [12].

Comparison of CRP levels with clinical severity was performed. Clinical severity was assessed by the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference Criteria [9], and patients were divided in the following groups: sepsis, severe sepsis and septic shock.

C-reactive protein, body temperature and white cells count (WCC) were measured at admission and then daily until discharge or death. The measurements of the day of sepsis diagnosis were used to predict outcome.

Measurement of CRP was performed by an immunoturbidimetric method (Tina-quant CRP; Roche Diagnostics, Mannheim, Germany).

We compared the clinical and laboratory data prospectively collected for survivors and nonsurvivors.

A similar a priori subgroup analysis was performed in patients with documented sepsis. Patients with documented sepsis were those with a defined source of infection who yield positive cultures.

Statistical analyses

The outcome measure was ICU mortality. Continuous variables are presented as mean ± standard deviation (SD). Differences in continuous variables were performed with the nonparametric Mann–Whitney *U*-test, unpaired Student's *t* test, one-way ANOVA or Kruskal–Wallis *H*-test. The Chi-square test was used to carry out comparisons between categorical variables. Numbers of patients were compared by Fisher's exact test. The correlation coefficient (r), coefficient of determination (r^2) or the Spearman rank correlation (r_s) was used to determine the relationship between two variables.

CRP levels were categorized in quintiles and compared with mortality rate. Linear regression analysis was used to compare SOFA with CRP levels.

Discrimination of APACHE II, SAPS II, SOFA, CRP, body temperature and WCC was tested to produce receiver-operating characteristic (ROC) curves. Areas under curves (AUC), with 95% confidence intervals (CI) were calculated in prediction of ICU mortality.

A P value below 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS 13.0 software.

Results

Patients characteristics

During the study period, 158 patients with the diagnosis of sepsis were consecutively included. Mean age was 59 ± 17 years, and 98 were males (Table 1).

Patients were divided according to ACCP/SCCM Consensus Conference criteria into the following groups: 12 patients with sepsis, 60 with severe sepsis and 86 with septic shock. Groups did not differ in sepsis aetiology. Amongst the septic patients, 61 (38.6%) had nosocomial infection; no significant differences were found between survivors and nonsurvivors (32.7 vs. 50%, $P = 0.052$).

Microorganisms were isolated in 76 (48%) septic patients being *Pseudomonas aeruginosa* the predominant microorganism (18, 24%).

The overall ICU mortality was 34.2% ($N = 54$). Nonsurvivors were older ($P = 0.005$) and tended to have higher APACHE II, SAPS II and SOFA scores ($P < 0.001$). Demographic and clinical data are summarized in Table 1.

Evaluation of CRP as prognostic marker of sepsis

C-reactive protein values varied from 2.4 to 85.4 mg/dL (median 24.2 mg/dL) and only 8 (5%) patients had CRP levels below 8.7 mg/dL [13].

We were unable to find any correlation between CRP concentrations and severity of sepsis ($r_s = 0.18$, $r_s^2 = 0.03$), as well as with the degree of organ failure assessed with the SOFA score ($r = 0.2$, $r^2 = 0.04$). We also assessed the influence of CRP levels in ICU mortality. Patients were divided in quintiles according to CRP values, <10, 10–20, 20–30, 30–40 and >40 mg/dL, and the associated mortality rate was 20, 34, 30.8, 42.3 and 39.1%, respectively ($P = 0.7$).

Table 1 Baseline characteristics of the patients with sepsis

	All ($n = 158$)	Survivors ($n = 104$)	Nonsurvivors ($n = 54$)	P values
Age (years)	58.6 ± 16.9	55.9 ± 17.1	63.8 ± 15.3	0.005
Sex (M/F)	98/60	63/41	35/19	0.656
APACHE II	21.2 ± 7.5	18.8 ± 6.3	26.0 ± 7.3	<0.001
SAPS II	47.2 ± 15.1	41.5 ± 11.7	58.2 ± 14.7	<0.001
SOFA	8.1 ± 3.6	6.7 ± 2.7	10.6 ± 3.6	<0.001
CRP (mg/dL)		25.3 ± 13.7	28.2 ± 13.1	0.15
Temperature (°C)		38.0 ± 0.9	37.9 ± 1.1	0.81
WCC (×1,000) mL^{-1}		15.4 ± 10.9	16.2 ± 13.7	0.7
Primary admission diagnosis (*N*)				0.289
Respiratory	64	46	18	
Cardiovascular	15	11	4	
Neurology	14	10	4	
Surgical	32	15	17	
Trauma	14	10	4	
Obstetrics	6	3	3	
Others	13	9	4	
Comorbidities (*N*)				
Neoplasm	21	12	9	
Chronic pulmonary disease	19	14	5	
Congestive heart failure	16	11	5	
Diabetes	9	6	3	
Ulcer disease	5	3	2	
Myocardial infarct	3	2	1	
Chronic renal disease	2	1	1	
Dementia	2	1	1	
Mild liver disease	1	0	1	
AIDS	1	0	1	

Values expressed in mean ± standard deviation
AIDS acquired immune deficiency syndrome

There were no differences between survivors and nonsurvivors in CRP levels, temperature and WCC (Table 1).

In a ROC analysis to distinguish between survivors and nonsurvivors, SAPS II had the highest AUC, 0.82 (95% CI 0.75–0.89), being significantly higher than the other studied variables ($P < 0.05$) with the exception of SOFA score (Table 2).

CRP as a prognostic marker in patients with documented sepsis

Seventy-six patients presented documented sepsis. The mean age was 59 years and 49 were males. The primary reason for ICU admission was respiratory failure ($N = 26$).

C-reactive protein values of these patients varied from 5.5 to 43.9 mg/dL (median 19.0 mg/dL). No differences were observed between survivors and nonsurvivors concerning APACHE II score (21.3 ± 6.3), body temperature (38.4 ± 1.1) and WCC (14.4 ± 8.2). However, the SAPS II and SOFA score were significantly higher in nonsurvivors (53.7 ± 13.7 vs. 42.5 ± 11.1, $P < 0.001$ and 9.8 vs. 6.2 ± 2.9, $P < 0.001$, respectively).

The AUC showed a good discriminative power in prediction of ICU mortality only for SAPS II (AUC 0.75, 95% CI 0.63–0.86) and SOFA score (AUC 0.77, 95% CI 0.66–0.88) (Table 2).

Table 2 Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) scores, serum C-reactive protein (CRP), body temperature and white cell count (WCC) of survivors and nonsurvivors of sepsis and documented sepsis

	Sepsis	Documented Sepsis
CRP (mg/dL)	0.55 (0.45–0.65)	0.66 (0.53–0.79)
Temperature (°C)	0.48 (0.38–0.58)	0.44 (0.29–0.59)
WCC (×1,000) mL^{-1}	0.46 (0.35–0.56)	0.6 (0.46–0.73)
APACHE II	0.75 (0.67–0.83)	0.65 (0.51–0.78)
SAPS II	0.82 (0.75–0.89)	0.75 (0.63–0.86)
SOFA	0.80 (0.72–0.88)	0.77 (0.66–0.88)

Discrimination is presented as area under receiver characteristics curve (AUC) with 95% confidence intervals (CI). Values expressed in mean ± standard deviation

Discussion

In our study, the prognosis of sepsis was assessed prospectively with measurements of CRP, body temperature and WCC, in order to identify patient's outcome. In this

context, we evaluated the correlation of CRP levels with sepsis severity, organ failure and ICU mortality and no correlation could be found. However, nonsurvivors tended to have higher APACHE II, SAPS II and SOFA scores, corresponding to a sicker population. In the subgroup of documented sepsis, we found similar results. Based on the present findings, CRP levels poorly predict outcome in terms of survival.

The levels of CRP have been shown to be well correlated with the severity of sepsis and other inflammatory diseases [14]. Chalmers et al. [15] demonstrated that low CRP levels at admission excluded severe community acquired pneumonia (CAP). Oberhoffer et al. [16] observed similar results in septic patients, finding good correlations with mortality with PCT and CRP.

However, some major studies found a poor correlation between CRP and mortality. Muller et al. [17] and Kruger et al. [18], studying CAP patients, found that CRP levels were not a good marker in predicting clinical severity of pneumonia assessed by Pneumonia Severity Score and CRB-65 score, respectively. Similarly, in septic patients, Pettila et al. [8] evaluated the performance of PCT, interleukin-6, CRP, WCC, D-dimer and antithrombin III in prediction of mortality and concluded that these biomarkers are not independently associated with hospital mortality.

The use of biomarkers in the assessment of prognosis of sepsis is a fundamental step for stratification of septic patients. In the present study, we were unable to find any correlation between severity of sepsis and CRP levels.

Besides, in assessing the correlation between CRP levels and organ dysfunction, we found that CRP was equally elevated irrespective of the SOFA score value. These results were similar to those found by Meisner et al. [19]. In opposition, Lobo et al. [20] found that CRP levels were correlated to higher SOFA scores. Our findings do not support the use of CRP, body temperature and WCC in prediction of outcome in critically ill septic patients. Nevertheless, our population had higher APACHE II and SOFA scores, as well as a larger subgroup of patients with septic shock.

Some limitations of the present investigation should be noted. First, this was a cohort single centre study and only ICU mortality was evaluated. Second, a mixed group of medical and surgical septic patients was examined. Finally, because we used clinical and microbiological evidence it might have been difficult to ascertain the precise cause of sepsis in all patients, and this might have introduced some misclassification bias.

Our study design had some distinctions: our main outcome was survival, a larger group of patients was included and we assessed a subgroup of patients with documented sepsis.

Conclusions

Our results demonstrate that despite CRP being a sensitive marker of infection, CRP of the day of sepsis diagnosis predicts poorly the survival outcome. According to our results we do not recommend the use of CRP level of the day of sepsis diagnosis as a marker of prognosis and risk stratification.

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6.2 Artigo 2: Should C-reactive protein concentration at ICU discharge be used as a prognostic marker?

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BMC Anesthesiology

RESEARCH ARTICLE Open Access

Should C-reactive protein concentration at ICU discharge be used as a prognostic marker?

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Abstract

Background: About one third of hospital mortality in critically ill patients occurs after Intensive Care Unit (ICU) discharge. Some authors have recently hypothesized that unresolved or latent inflammation and sepsis may be an important factor that contributes to death following successful discharge from the ICU.

Aim: The aim of our study was to determine the ability of the clinical and inflammatory markers at ICU discharge to predict post-ICU mortality.

Methods: A prospective observational cohort study was conducted during a 14-month period in an 8 bed polyvalent ICU. Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment (SOFA) score, Therapeutic Intervention Scoring System-28 (TISS-28), C-reactive protein (CRP), white cell count (WCC) and body temperature of the day of ICU discharge were collected from patients who survived their first ICU admission.

Results: During this period 156 patients were discharged alive from the ICU. A total of 29 patients (18.6%) died after ICU discharge. There were no differences in clinical and demographic characteristics between survivors and nonsurvivors. C-reactive protein levels at ICU discharge were not significantly different between survivors and nonsurvivors. The area under receiver operating characteristics curves of APACHE II, SAPS II, SOFA, TISS-28, CRP, WCC and body temperature at ICU discharge as prognostic markers of hospital death were 0.76 (95% confidence interval (CI) 0.67-0.86); 0.75 (95% CI 0.66-0.85); 0.72 (95% CI 0.62-0.83); 0.64 (95% CI 0.52-0.77); 0.55 (95% CI 0.43-0.67); 0.55 (95% CI 0.42-0.66) and 0.54 (95% CI 0.44-0.67) respectively. The hospital mortality rate of the patients with CRP <5, 5-10, >10 mg/dL was 15.1%, 16.1% and 33.3% respectively (p = NS).

Conclusions: At ICU discharge serum CRP concentration was a poor marker of post-ICU prognosis. Post-ICU death appears to be unrelated to the persistent inflammatory response.

Background

Critically ill patients are responsible for 10-25% global hospital costs [1]. The ability to identify critically ill patients who will not survive until hospital discharge may allow identification of high risk patients leading to more conservative strategies of ICU discharge.

About one third of hospital mortality of critically ill patients occurs after Intensive Care Unit (ICU) discharge [2].

Smith et al. observed in 283 patients discharged from the ICU to hospital wards that patients with higher Therapeutic Intervention Scoring System (TISS)-28 had higher post-ICU mortality (TISS-28 >20 = 21.4% vs. TISS-28 <10 = 3.7%, p < 0,0001) [3]. Several other risk-prediction models have been used to predict in-hospital mortality after patient discharge from the ICU [4,5]. However risk estimated by these models showed considerable variation across the disease spectrum of ICU patients.

Post ICU deaths arise mainly as a result of incomplete resolution of the primary condition or from the development of new complications [6-8]. Some authors have recently hypothesized that unresolved or latent inflammation and sepsis may be an important factor that

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contributes to death following successful discharge from the ICU [6].

In two recent studies with critically ill patients, a high CRP concentration at ICU discharge was associated with a subsequent increase in in-hospital mortality [6,9].

The aim of our study was to determine the ability of the clinical and inflammatory markers at ICU discharge to predict post ICU mortality.

Methods

This study was a prospective, single center, observational study conducted during a 14-month period in the ICU of Garcia de Orta Hospital, an 8-bed multidisciplinary ICU.

The Hospital Ethics Committee approved the study design, and informed consent was waived because this was an observational study without any deviation from the current medical practice.

Patients were included in the study if they were discharged alive from the ICU and if they were more than 17 years old. Discharged criteria were clinical improvement without need of further organ support and/or intensive monitoring. Patients were followed until hospital death or hospital discharge. Only the first ICU admission was included.

The clinical predictors analyzed included Acute Physiology and Chronic Health Evaluation (APACHE) II [10], Simplified Acute Physiology Score (SAPS) II [11], Sequential Organ Failure Assessment scores (SOFA) [12] and Therapeutic Intervention Scoring System-28 (TISS-28) [13].

C-reactive protein, body temperature and white cells count (WCC) were measured at admission and then daily until discharge.

Measurement of CRP was performed by an immunoturbidimetric method (Tina-quant CRP; Roche Diagnostics, Mannheim, Germany).

We compared the clinical and laboratory data of survivors and nonsurvivors after ICU discharge.

A subgroup analysis between infected and non-infected patients was performed. Surgical and medical patients were also analyzed. We considered that the patient belong to the surgical group if the main reason of ICU admission was surgical, obstetric or trauma.

Statistical Analyses

The outcome measure was post-ICU mortality. Continuous variables are presented as mean +/- standard deviation (SD), unless stated otherwise. Differences in continuous variables were performed with the parametric unpaired Student's *t* test and one-way ANOVA or with the nonparametric Mann-Whitney *U*-test or Kruskal-Wallis *H*-test according to data distribution. The Chi-square test was used to carry out comparisons between categorical variables.

C-reactive protein levels were categorized in three groups (CRP <5, 5-10, >10 mg/dL) and compared with mortality rate. Linear regression analysis was used to compare SOFA with CRP levels. Discrimination of APACHE II, SAPS II, SOFA, TISS-28, CRP, body temperature and WCC was tested to produce receiver-operating characteristic (ROC) curves. Areas under curves (AUC), with 95% confidence intervals (CI) were calculated in prediction of ICU mortality. A p value below 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 16.0 software.

Results

During a 14-month period a total of 262 patients were admitted in the ICU. The overall ICU mortality was 40%.

One hundred and fifty six patients were discharged alive from ICU to ward with a mean age of 55 ± 18 and 93 (60%) were males (Table 1).

A total of 29 patients (18.6%) died in hospital after ICU discharge. Clinical and demographic characteristics of post-ICU survivors and nonsurvivors are presented in table 1. The mean duration of follow-up post-ICU discharge was 34.8 days, with no difference between survivors and nonsurvivors (34.3 ± 26.8 versus 37.6 ± 24.9 days; p = NS). Nonsurvivors were sicker with higher levels of APACHE II, SAPS II, SOFA and TISS-28. (Table 1).

C-reactive protein was determined in all patients at ICU discharge. C-reactive protein values varied from 0.15 to 43.5 mg/dL.

Although 25% higher in nonsurvivors, CRP levels at ICU discharge was not significantly difference in relation to survivors (survivors - 8.1 ± 8.0 vs. nonsurvivors - 10.2 ± 12.0 mg/dL; p = NS). In addition, no correlation could be found between higher CRP levels and mortality. Post-ICU mortality rate of the patients with CRP <5, between 5-10, >10 mg/dL was 15.1% (N = 9), 16.1% (N = 9) and 33.3% (n = 11) respectively (p = NS).

The area under the ROC curves of APACHE II, SAPS II, TISS-28, SOFA, CRP, WCC and body temperature and at ICU discharge as prognostic markers of post-ICU death were 0.76 (95% CI 0.67-0.86), 0.75 (95% CI 0.67-0.86), 0.72 (95% CI 0.62-0.83), 0.64 (95% CI 0.52-0.77), 0.55 (95% CI 0.43-0.68), 0.56 (95% CI 0.44-0.67) and 0.54 (95% CI 0.44-0.67) respectively (Figure 1).

CRP as a prognostic marker in patients with previous documented infection

One hundred and thirty six out of 262 of the patients discharged from ICU presented at least one documented

Table 1 Baseline characteristics of the patients discharged from the Intensive care Unit

	All (n = 156)	Survivors (n = 127)	Nonsurvivors (n = 29)	*p* values
Age, yrs	55 ± 18	53 ± 19	62 ± 12	NS
Sex (M/F)	93/63	79/48	14/15	NS
APACHE II	14.6 ± 6.2	13.4 ± 5.3	20.0 ± 7.1	<0.001
SAPS II	28.6 ± 12.7	25.9 ± 9.6	40.5 ± 17.5	<0.001
TISS-28	25.1 ± 5.3	24.2 ± 4.3	28.8 ± 7.1	<0.001
SOFA	3.5 ± 2.7	3.0 ± 1.8	5.6 ± 4.7	<0.001
CRP (mg/dL)	8.5 ± 8.3	8.1 ± 8.0	10.1 ± 9.5	NS
Temperature (ºC)	36.9 ± 2.7	36.8 ± 3.0	37.2 ± 0.8	NS
WCC (x1000)/mL	11.3 ± 7.4	10.6 ± 6.0	14.4 ± 11.4	NS
Admission diagnosis (N)				
Respiratory	47	35	12	
Trauma	24	21	3	
Surgical	21	17	4	
Cardiovascular	21	17	4	
Neurological	14	13	1	
Obstetrics	6	6	0	
Gastroenterological	6	5	1	
Others	17	13	4	

Values expressed as mean ± standard deviation

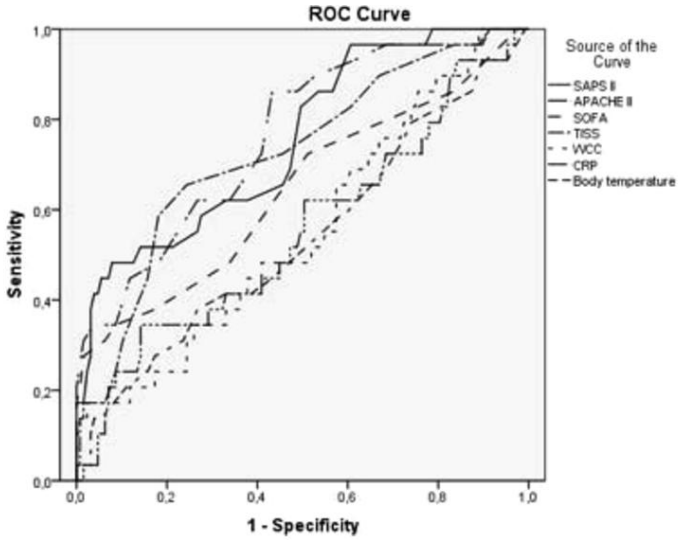

Figure 1 Receiver operating characteristics (ROC) curves of Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE) II, Therapeutic Intervention Scoring System-28 (TISS-28), Sequential Organ Failure Assessment (SOFA) scores, serum C- reactive protein (CRP), body temperature and white cell count (WCC).

Table 2 Baseline characteristics of the patients with documented infection

	Survivors (n = 127)	Nonsurvivors (n = 29)	*p* values
Age, yrs	54 ± 18	62 ± 12	*p* = NS
Sex (M/F)	69/39	14/14	*p* = NS
APACHE II	13.7 ± 4.9	20.3 ± 10.0	*p* < 0.001
SAPS II	26.2 ± 8.8	41.3 ± 17.2	*p* < 0.001
TISS-28	24.1 ± 3.6	29.1 ± 7.1	*p* < 0.001
SOFA	3.0 ± 1.7	5.7 ± 4.7	*p* < 0.001
CRP (mg/dL)	8.4 ± 8.2	10.3 ± 9.6	*p* = NS

Values expressed as mean ± standard deviation

infection during their ICU stay. The mean age was 55 ± 17 years and 83 (61%) were males.

The primary reason for ICU admission was respiratory failure due to pneumonia. The in-hospital mortality rate from the patients with documented infection was 21%.

At ICU discharge, CRP values varied from 0.15 to 43.5 mg/dL (median 5.7 mg/dL). No differences in CRP levels were observed between survivors and nonsurvivors (8.4 ± 8.2 vs. 10.3 ± 9.6 mg/dL, p = NS, respectively) after discharge. However, the SAPS II, APACHE II, TISS-28 and SOFA score were significantly higher in nonsurvivors (Table 2).

The AUC showed a good discriminative power of post-ICU mortality for TISS-28 (AUC 0.75; 95% CI 0.665-0.86), SAPS II (AUC 0. 77; 95% CI 0.68-0.87) and APACHE II score (AUC 0.78; 95% CI 0.68-0.87). For CRP levels the AUC did not demonstrate a good discriminative power of post-ICU mortality (AUC 0.55; 95% CI 0.42-0.67).

CRP as a prognostic marker in surgical and medical patients

In 51 patients the main admission diagnosis was surgical. The mean age was 49 ± 19 years and 33 (65%) were male.

The post-ICU mortality rate was 14% and no differences were observed between surgical and medical patients.

C-reactive protein levels at ICU discharge were significantly higher than in medical patients (6.5 ± 7.0 vs. 12.5 ± 9.2; p < 0.001). However no differences in CRP levels at ICU discharge could be found between survivors and nonsurvivors in both surgical and medical patients (5.9 ± 6.7 mg/dL vs. 8.7 ± 8.9 mg/dL; *p* = NS and 12.2 ± 8.6 mg/dL vs. 14.6 ± 13.0; *p* = NS, respectively).

CRP also did not demonstrate a good discriminative power of post-ICU mortality (Medical Group: AUC 0. 51; 95% CI 0.19-0.82 and Surgical Group: AUC 0.38; 95% CI 0.24-0.52).

Discussion

In this prospective observational study with 156 patients discharged alive from ICU, we evaluated the relation between CRP levels at ICU discharge and post-ICU mortality. Our data demonstrate that CRP at ICU discharge was not correlated with in-hospital mortality. Even in patients with higher levels of CRP (>10 mg/dL) there was no significant increase in post-ICU mortality. In the subgroup analysis these data were similar and no association could be found between CRP levels and post-ICU mortality in patients with previous documented infection and in medical and surgical patients.

In a heterogeneous ICU patient population, Lobo et al. showed that admission CRP levels correlated with an increased risk of organ failure and death [14]. In addition, our group showed that persistently elevated CRP concentrations in infected critically ill patients were associated with poor outcome [15,16]. Recently, it has been described that in survivors of an acute infection could present a state of persistent inflammation that may lead to deterioration of other diseases, such as cardiovascular disease, and an increased long-term mortality [7].

Long-term mortality has been assessed in a recent multicenter study conducted by Yende et al. [8]. Authors included 1799 patients discharged from emergency department with a primary diagnosis of community pneumonia. Interleukin-6 (IL-6) concentrations at hospital discharge were higher among subjects who did not survive at 100 days compared with those who survived (12.9 vs. 6.6 pg/mL, p < 0.001). This difference was not obtained among those who did and did not survive between 101 days and 1 year (7.7 vs. 6.5 pg/mL, p = NS). However, nonsurvivors compared with survivors at 1 year, nonsurvivors were older, had more co-morbid conditions, as evidenced by higher Charlson scores, and had more severe CAP on presentation, as evidenced by higher Pneumonia Severity Index and APACHE III scores.

In a recently published study by Ho et al. [6], that analyzed short-term mortality among ICU patients, a significant association between CRP concentrations at ICU discharge and subsequent in-hospital mortality was identified. In this prospective cohort study of 603 consecutive patients who survived their first ICU admission, CRP concentrations at ICU discharge were associated with subsequent in-hospital mortality in the univariate analysis (non-survivors -17.4 vs. survivors - 8.56 mg/l, p = 0.001).

In our study we were unable to reproduce these findings, since CRP was a poor prognostic marker of post-ICU mortality (AUC 0.55; 95% CI 0.42-0.67). However, in Ho et al. study [6], CRP concentrations were available only in 73% of the nonsurvivors and the number of unexpected post-ICU deaths was small (4.3%). Hence the results could be imprecise and may not be extrapolated to ICUs with higher post-ICU mortality rates.

In opposition, our data does not support the use of CRP in outcome prediction in critically ill patients,

however, in comparison with Ho et al. data, our population had higher APACHE II, SOFA scores and TISS-28 as well as a larger subgroup of patients with documented infection.

In a recently published study, we also could not found a relation between CRP levels of the day of sepsis diagnosis and ICU survival [17]. Both these results demonstrate that, despite CRP has been repeatedly shown to be a sensitive marker of infection; it predicts poorly the patient outcome.

Our study has some limitations. First, this was a cohort single centre study with only 8 beds of intensive care. Second a mixed group of medical and surgical patients were included; whether CRP will have a better performance in a particular subgroup of patients, for example in patients with lower respiratory tract infection remains uncertain, but deserves further investigation. Finally severity scores were used at ICU discharge, however these scores were only developed and validated to be used in the first 24 hours after ICU admission.

Our study design had some distinctions: we analyzed separately the patients with previous documented infection as well as medical and surgical patient, and patients with end-life limitations were not excluded.

Conclusions

Some studies suggest that persistent inflammation may precipitate deterioration in other diseases, such as cardiovascular disease, and increase long-term mortality [7]. In our data no correlation between CRP concentrations at ICU discharge and post-ICU hospital mortality could be found, with post-ICU survival appearing to be unrelated to higher levels of inflammatory biomarkers. Reasons for increased long and short - term mortality among ICU survivors are not fully understood. As a result, future studies are needed to explore the relationship between biomarkers on subsequent health-related outcomes.

Key messages

- In the present study C-reactive protein concentrations at ICU discharge were not related to post-ICU hospital outcome. C-reactive protein despite being a sensitive marker of infection, it predicts poorly the patient outcome.
- Similar results were observed in the subgroup of ICU survivors with documented infection.
- C-reactive protein also did not demonstrate a good discriminative power of post-ICU mortality between medical and surgical patients.

List of abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; AUC: Areas under curves; CI: Confidence intervals; CRP: C-reactive protein; ICU: Intensive Care Unit; ROC: Receiver-operating characteristic; SAPS: Simplified Acute Physiology Score; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; TISS-28: Therapeutic Intervention Scoring System-28; WCC: White cell count.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors conceived the study. PP and LC collected the data. JS and PP drafted the manuscript. All authors helped with manuscript drafting and approved the final manuscript.

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6.3 Artigo 3: Impact of fulminant hepatic failure in C-reactive protein?

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Impact of fulminant hepatic failure in C-reactive protein?

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Keywords:
C-reactive protein;
Infection;
Sepsis;
Fulminant hepatic failure

Abstract
Introduction: Fulminant hepatic failure (FHF) refers to the rapid development of severe acute liver injury with impaired synthetic function, coagulopathy, and encephalopathy in a person who previously had a normal liver or had a well-compensated liver disease. It is a rare complication in critically ill patients and carries a very bad prognosis. Serum C-reactive protein (CRP), a useful marker of infection, is produced exclusively by the liver.
Aim: The aim of this study was to assess CRP concentrations in patients with FHF.
Methods: We prospectively identified patients with sepsis and FHF treated at the intensive care unit (ICU). Data collected included admission diagnosis, medical history, systemic inflammatory response syndrome criteria, Acute Physiologic and Chronic Health Evaluation II, and Sequential Organ Failure Assessment scores. C-reactive protein and white cell count were measured at admission and then daily until ICU discharge.
Results: We included 7 patients with FHF and sepsis. Six patients died with severe multiple organ failure. Six patients were already admitted with FHF, with the remaining one being diagnosed at the 26th day of ICU stay. All patients present severe coagulopathy. In all septic patients, despite clinical deterioration, CRP levels were markedly decreased sometimes reaching undetectable levels.
Conclusion: In septic patients with FHF, CRP is more a marker of severe liver dysfunction and should not be used as a marker of infection. As a result, in a patient admitted with a very high suspicion of infection and an abnormally low CRP concentration or with a marked CRP decline despite persistent septic shock, severe hepatic failure should be ruled out.

1. Introduction

Fulminant hepatic failure (FHF) refers to the rapid development of severe acute liver injury with impaired synthetic function, coagulopathy, and encephalopathy in a person who previously had a normal liver or had well-compensated liver disease [1]. Fulminant hepatic failure is a rare but potentially catastrophic condition for which liver transplantation is the only definitive and effective therapy

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[2]. However, even in the transplanted patients mortality remains high, reaching 40% [3].

The most prominent causes of FHF are drug-induced liver injury, namely, acetaminophen, viral hepatitis, autoimmune liver disease, and shock or hypoperfusion. Often FHF affects young patients and carries a high morbidity and mortality.

Inflammation, infection, tissue injury/necrosis, or surgical trauma induce local and systemic physiologic changes known as the acute phase response to limit the progression of the injury and protect the organism against further damage [4].

The liver is pivotal in modulating the systemic response to severe infection [5]. In sepsis, the liver has 2 opposing roles, because it is a main source of inflammatory mediators but also a target organ for the effects of the inflammatory mediators [6-8], In FHF, synthesis capability is greatly compromised secondary to the severe liver damage [9].

Serum C-reactive protein (CRP) is an acute phase protein exclusively synthesized by the liver primarily in response to interleukin-6 [4]. It is secreted in increased amounts within 6 hours of an acute inflammatory stimulus [10]. The plasma concentration can double at least every 8 hours, reaching a peak after approximately 50 hours [4,11-13].

C-reactive protein is a very commonly used marker of infection [14,15]. However, its course in patients with FHF has not been well described. The aim of the present study was to evaluate 7 patients with FHF and severe sepsis or septic shock.

2. Methods

We prospectively identified patients with FHF and sepsis treated at the intensive care unit (ICU) of our institution between November 2001 and January 2009. Patients were included if they fulfilled the criteria for FHF and sepsis.

Fulminant hepatic failure was defined according to Trey and Davidson [16] criteria as an acute deterioration of liver function resulting in development of encephalopathy within 8 weeks of the onset of symptoms in a patient with a healthy liver.

Sepsis was considered according to the definitions of the Centers for Disease Control and Prevention [17,18]. Only the first episode of severe liver dysfunction in each septic patient was considered.

Severity of illness was assessed by calculating Acute Physiologic and Chronic Health Evaluation II score [19] and the assessment of organ dysfunction/failure with the Sequential Organ Failure Assessment score [20].

Measurement of CRP was performed by an immunoturbidimetric method (Tina-quant CRP; Roche Diagnostics, Mannheim, Germany).

2.1. Patient 1

Patient 1 was a 63-year-old man admitted in the emergency department (ED) with a 2-day history of muscle cramps, nausea, anorexia, and altered consciousness (Table 1). He had a medical history of type 2 diabetes mellitus and arterial hypertension and was a chronic B viral hepatitis carrier. The clinical and radiologic findings were compatible with the diagnosis of severe community-acquired pneumonia with a CURB 65 (Confusion, Urea, Respiratory rate, Blood pressure and age 65) score of 4. His clinical condition deteriorated rapidly with respiratory and cardiac arrest requiring advanced life support, being later transferred to our ICU. At ICU admission, the patient presented severe septic shock with multiple organ failure (renal, hepatic, respiratory, hemodynamic, and hematologic failure). Antibiotic therapy was

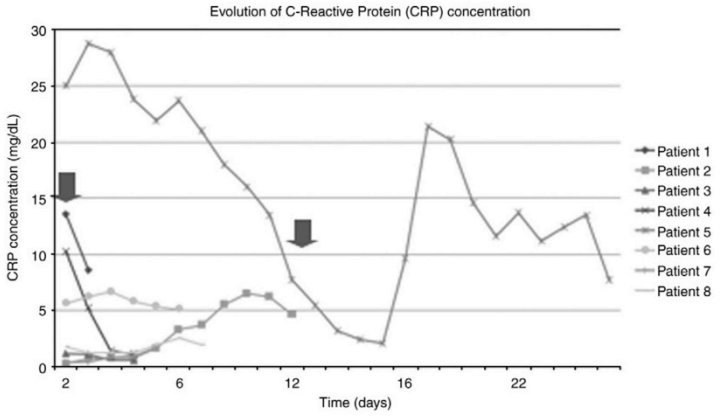

Fig. 1 C-reactive protein concentration course during ICU stay (arrow indicates the day of FHF diagnosis).

started with piperacilin/tazobactam associated with claritromycin. The patient also received respiratory, renal, and vasopressor support. He died the following day. The blood profile is presented in Table 2 and Fig. 1.

2.2. Patient 2

Patient 2 was a 51-year-old man, admitted in the ED with seizures. He had a 24-hour history of fever without other accompanying symptoms. He had a history of alcohol abuse, and there was a possible contact with the urine of several nondomestic animals. At the time of admission, the patient presented a generalized jaundice without other significant findings. From the blood profile, he presented severe alterations in the hepatic function and a very low CRP level (Tables 1 and 2 and Fig. 1). The head and abdominal computed tomography scans were normal. A lumbar puncture was performed, and the result was also normal. A leptospirosis diagnosis was considered, and treatment with ceftriaxone and doxycycline was started. The diagnosis was confirmed 2 weeks later by serology. On the second day, his clinical condition deteriorated and he was transferred to the ICU. At ICU admission, the clinical diagnosis of an FHF was considered. The patient remained with the same antibiotics and also received respiratory, renal, vasopressor, and transfusional support.

On the sixth day of treatment, his clinical condition had improved and was discharged at day 10 of ICU stay. Two weeks later after ICU discharge, the patient received a liver transplant and was discharged from the hospital.

2.3. Patient 3

Patient 3 was a 24-year-old woman with a medical history of pulmonary tuberculosis diagnosed 1 month before hospital admission, being treated with antituberculosis drugs: isoniazid (5 mg kg^{-1} d^{-1}), rifampin (10 mg kg^{-1} d^{-1}), pyrazinamide (20 mg kg^{-1} d^{-1}), and ethambutol (15 mg kg^{-1} d^{-1}). She was transferred to the ICU with acute respiratory failure, hypotension, and high fever. Diffuse bilateral pulmonary infiltrates were visible on the chest x-ray. At the time of admission, the patient presented low level of consciousness, with a general jaundice, requiring mechanical ventilation and vasopressor support. Septic shock was considered. The blood profile indicated severe alterations in the hepatic function and a low CRP level (Table 2 and Fig. 1).

A diagnosis of FHF was considered. During the ICU stay, the patient presented a severe refractory shock and died on the third day.

2.4. Patient 4

Patient 4 was a 42-year-old healthy man who was admitted in the ED with fever and a severe pain in his left

Table 1 General characteristics of the patients with sepsis and FHF

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (y)	63	51	24	42	45	69	43
Sex	Male	Male	Female	Male	Female	Male	Male
Admission diagnosis	Severe community-acquired pneumonia	Leptospirosis	Acute respiratory failure	Septic arthritis with necrotizing fasciitis	Severe community-acquired pneumonia-	Acute abdomen with peritonitis	Severe malaria
Comorbidities	AgHBs+ Hypertension Diabetes	Alcoholism	Pulmonary tuberculosis	None	Hepatitis C carrier	AgHBs+ Chronic liver failure Hypertension COPD Alcoholism Chronic atrial fibrillation	None
Length ICU stay, days	0.4	10.0	3.3	2.6	23.8	5.3	0.2
APACHE II	Not applicable[a]	21	29	30	12	23	Not applicable[a]
Time to FHF	Admission	Admission	Admission	Admission	26th day	Admission	Admission

HBsAg+ indicates hepatitis B antigen; COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation.
[a] APACHE II was not determined because patients remained less than 24 hours in the ICU.

Table 2 Laboratory values of the patients with sepsis and FHF

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7	
	Admission	ICU discharge	Admission	ICU discharge	Admission	ICU discharge	Admission	ICU discharge	Admission	ICU discharge	Admission	ICU discharge	Admission	ICU discharge
CRP (mg/dL)	13.6	8.61	0.3	4.7	1.2	0.6	8.0	3.1	25.0	6.1	5.7	5.1	23.6	4.4
Fibrinogen (mg/dL)		204	60	218	110	60	78	85	366	111	132	122	Undetectable	Undetectable
Factor V (%)	23	23	3	71	–	7	–	5	–	16	–	18		0.4
Platelets (/mL)	53 000	40 000	15 000	80 000	82 000	127 000	36 000	41 000	70 000	37 000	62 000	40 000	8000	10 000
Bilirrubin (mg/dL)	6.72	5.36	3.45	21.5	15.2	16.7	4.2	6.2	1.3	35.7	13.3	18	2.8	1.8
AST (IU/L)	143	483	2124	172	174	263	1175	14623	42	535	424	356	–	–
ALT (IU/L)	87	154	1281	203	88	112	483	2879	112	38	132	169	224	701
SOFA	18	15	18	15	11	16	16	15	11	17	10	12	18	18

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; SOFA, Sequential Organ Failure Assessment.

knee. A knee ultrasound revealed the presence of intraarticular fluid, and an arthrocentesis was performed with the identification of pus. Septic arthritis caused by a β-hemolytic Streptococcus was diagnosed. Two days later, the patient developed a compartment syndrome with necrotizing fasciitis and myonecrosis that rapidly evolved to septic shock with multiple organ failure (respiratory, renal, cardiovascular, and hepatic failure) and was admitted in the ICU. A decompressive fasciotomy was performed. During the ICU stay, the patient presented a septic shock with severe lactic acidosis and died on the fifth day. The blood profile is presented in Table 2 and Fig. 1.

2.5. Patient 5

Patient 5 was a 45-year-old woman who was admitted to the hospital with the diagnosis of community-acquired pneumonia. Two weeks before admission, an upper respiratory tract infection was diagnosed. At the time of hospital admission, her clinical condition had markedly deteriorated and the patient was intubated and transferred to the ICU. Empiric antibiotics with piperacilin/tazobactam and erytromycin were initiated. On the second day of ICU stay, she developed septic shock. After 10 days of antibiotic therapy, the patient evolved to FHF. Serology for viral hepatitis revealed that the patient presented C hepatitis. *Serratia marcescens* was isolated from bronchoalveolar lavage and blood cultures with susceptibility only to imipenem-cilastatin. Antibiotics were changed accordingly. Her condition did not improve, and the patient died on the 26th day.

A postmortem liver biopsy was performed and revealed extensive hepatic necrosis associated with a cholestasis pattern.

The blood profile is presented in Table 2 and Fig. 1.

2.6. Patient 6

Patient 6 was a 69-year-old man with a medical history of hypertension, chronic bronchitis, and atrial fibrillation that was admitted in the hospital for an elective surgery. The patient was submitted to a left hemicolectomy due to a colonic adenocarcinoma.

After surgery, the patient developed a septic shock with respiratory, renal, cardiovascular, and hepatic failure. The blood profile is presented in Table 2 and Fig. 1.

The patient performed an abdominal computed tomography scan that revealed a right bowel obstruction. The patient was submitted to a second laparotomy, and the mechanical obstruction was resolved. During the ICU stay, the hepatic function deteriorated and the patient died on the fifth day.

2.7. Patient 7

Patient 7 is a 43-year-old man admitted in the ICU with a diagnosis of severe malaria. The patient had returned 10 days before from Angola where he had been working for 10

months. He had no previous comorbidities and never performed malaria prophylaxis. Two days later, the patient went to an ED with high fever, and diagnosis of malaria was performed, but the patient refused treatment and was discharged against medical advice. Six days later, he was admitted in our ICU with septic shock with multiple organ dysfunction (respiratory, cardiovascular, hepatic, renal failure). The patient was ventilated and received renal and vasopressor support. *Plasmodium falciparum* was identified from blood smear. Sulphate quinine, doxycycline, and exchange blood transfusion were also started. He died in the first hours after ICU admission. The blood profile is presented in Table 2 and Fig. 1.

3. Results

During the study period, we enrolled 7 patients with sepsis and acute FHF. Of these 7 patients, 6 died in severe multiple organ failure and 1 received a liver transplant. Characteristics of the patients are summarized in Tables 1 and 2.

Most patients (6 patients) were already admitted with FHF, whereas in 1 patient, FHF was diagnosed at 26th day of ICU stay (Fig. 1). In our case series, 1 patient presented a history of documented chronic hepatic disease and another had a history of alcohol abuse but no documented hepatic disease.

All patients were sedated and mechanically ventilated on the time of admission making the correct assessment of encephalopathy impossible.

Severe coagulopathy and elevated bilirrubin were observed in all patients. Only 2 patients showed marked elevation of hepatic enzymes (Table 2).

In all patients, despite clinical deterioration, CRP levels markedly decrease to normal levels. All of our patients presented CRP levels below 10 mg/dL at the time of FHF diagnosis (Table 2 and Fig. 1).

4. Discussion

In this case series of very severe septic patients, we analyzed the usefulness of CRP as a marker of infection.

In FHF, hepatic proteins synthesis ability is greatly reduced, namely, factor V and other coagulation factors, the coagulation inhibitors like antithrombin III, protein C, protein S, heparin cofactor II, and the protease inhibitor a_1-antitrypsin [21,22].

Izumi et al [9] studied the acute phase response in 50 FHF patients evaluating several acute phase proteins, namely, CRP. They demonstrated that in FHF, CRP concentrations were markedly lower than expected for such a severe inflammatory stimulus.

Some mechanisms, alone or in combination, may explain these findings: serum CRP is exclusively produced by the liver, and their production in FHF may already be at maximal rate, being limited by the severe loss of hepatic synthetic function as part of the inflammatory response to the liver cell injury [9].

Concerning the use of CRP in patients with liver disease, there are studies with conflicting results. Some authors advocate that CRP has a weak predictive power of infection in patients with decompensated cirrhosis [23]. However, a recent study of Bota et al [24] demonstrated in 79 critically ill patients with cirrhosis that CRP and procalcitonin were good markers of documented infection with an area under receiver operating curve of 0.72 and 0.70, respectively. In addition, no differences in CRP concentrations were found between these patients and those without cirrhosis.

In a recent study by Rahman et al [25] with 138 patients submitted to major liver resection, the 11 patients who developed septic complications were among the 48 patients with a CRP level of 3.2 mg/dL or less. The authors also observed that serum CRP levels were significantly lower in patients who developed persistent hyperbilirubinemia, ascites, encephalopathy, and coagulopathy.

However, in none of these studies, the authors assessed the impact of FHF on biomarkers' levels. Consequently, in this group of patients, the behavior of CRP as an indicator of infection was still obscure.

In our study, we present the largest series of patients with FHF and septic shock. In all, very low levels of factor V activity documented hepatic failure. We also observed that despite clinical deterioration, CRP levels were markedly decreased despite the presence of refractory septic shock. Moreover, in our case series, at the time of FHF diagnosis, all patients presented low factor V activity associated with low CRP levels.

Hepatic failure is difficult to assess in critical care patients. Some devices, like Liver Function Monitor (LiMON), are being studied in the prediction and early detection of posthepatectomy liver failure [26]; however, no data documented any benefit in monitoring the development of FHF in septic patients.

In view of these findings, we propose that in FHF, CRP is more a marker of severe liver dysfunction and should not be used as marker of infection.

In addition, we also propose that in a patient with a very high suspicion of infection and an abnormally low CRP level, the presence of FHF should be ruled out, namely, assessing factor V activity.

The utility and usefulness of a biomarker are also linked to the complete knowledge of its biology, strengths, limitations, and confounders. In the critical care setting, it is necessary to know the effect on the biomarker level of different therapies and interventions, namely, steroids and renal replacement therapy [27-29]. Concerning FHF, it is also important to know the behavior of biomarkers. The present study adds further information concerning CRP in patients with severe sepsis and septic shock and FHF.

5. Conclusions

C-reactive protein levels in a patient with FHF should not be used as a marker of infection due to the severe loss of hepatic synthetic function. Conversely, hepatic failure should be ruled out in a patient with a high suspicion of infection and abnormally low CRP levels.

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6.4 Artigo 4: Assessment of risk factors for in-hospital mortality after intensive care unit discharge

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RESEARCH ARTICLE

Assessment of risk factors for in-hospital mortality after intensive care unit discharge

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Abstract

Context: Post-intensive care unit (ICU) mortality predictors are unknown.

Objective: To assess post-ICU in-hospital mortality predictors.

Materials and methods: Analysis of 296 patients discharged alive from a medical-surgical ICU during an 18-month period.

Results: Post-ICU in-hospital mortality was 22.6%. Nonsurvivors had significantly higher Charlson comorbidity score and more often had a tracheostomy. C-reactive protein (CRP) "alert measurement", ≥6 mg/dL, independently discriminated survivors from nonsurvivors.

Discussion: A CRP "alert measurement" or the need for tracheostomy may be used to identify patients with high risk of dying after ICU discharge.

Conclusions: Charlson comorbidity score, CRP and tracheostomy predicted post-ICU in-hospital mortality.

Keywords: ICU patient discharge, mortality, C-reactive protein, tracheostomy, Charlson comorbidity score

Introduction

The population of patients admitted to Intensive Care Units (ICU) is predicted to grow in the next years (Adhikari et al., 2010) including a large proportion that will ultimately die. In a recent study, ICU mortality ranged from 10.1 to 27.3%, depending on the case-mix, the country and the continent (Vincent et al., 2009). A great effort has been made to identify risk factors associated with ICU and, in particular, in-hospital mortality. Several scores have been developed, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score (Knaus et al., 1981), the mortality probability models (Lemeshow et al., 1988), the Simplified Acute Physiology Score (SAPS) II (Le Gall et al., 1993), and more recently the SAPS3 (Moreno et al., 2005), among others. Almost all severity scores use a group of demographic, clinical and physiological variables from the first day of ICU stay to obtain an individual patient score and a prediction of in-hospital mortality.

Usually the above mentioned severity scores are used to monitor the performance of a single ICU, to adjust mortality of different ICUs to its case-mix and for helping in guiding resource allocation (Gunning and Rowan, 1999). The currently available models are not useful and were not designed as well as validated for individual patient management (Cullen and Chernow, 1994).

Besides, a substantial percentage of patients, ranging from 4.3 to 31%, die in the wards after ICU discharge (Moreno et al., 1998, Ho et al., 2008). Furthermore, it has been shown that those patients not only had higher ICU lengths of stay (LOS) but also a higher resource consumption (Stricker et al., 2003). Although some patients are discharged from ICU with a plan to limit life support, others die unexpectedly and this seems not to be related

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to treatment deficiencies (Lawrence and Havill, 1999). Discharge of high-risk patients to high-dependency units may theoretically prove to be useful and to reduce mortality.

However, risk factors of post-ICU in-hospital mortality have been scarcely studied. Besides, the above mentioned severity scores were not developed specifically for this evaluation and are not helpful in such assessment. The aim of our study was to assess risk factors easily available at ICU discharge of post-ICU in-hospital mortality.

Methods

We performed a single center, retrospective, observational study with prospectively collected data, conducted during an 18-month period, between January 2008 and June 2009. The local Ethics Committee approved the study design.

All patients discharged alive from the São Francisco Xavier Hospital medical-surgical ICU were included in the study. Patients requiring continuous monitoring and/or intermediate care were discharged to high-dependency units; all other patients were discharged to medical or surgical wards. Only patients discharged home directly from ICU were excluded.

Follow-up was conducted until in-hospital death or hospital discharge. If a patient was readmitted to the ICU during the same hospitalization, only the first ICU admission was considered.

Data collected included demographic characteristics (age, gender); SAPS II; Charlson comorbidity score (Charlson et al., 1987); ICU and hospital LOS; diagnosis of infection during ICU stay; presence and duration of mechanical ventilation, of continuous renal replacement therapy and of central venous catheterization; presence of tracheostomy at the time of ICU discharge; concentration of C-reactive protein (CRP), haemoglobin and platelet count at the day of ICU discharge; discharge period (night – from 8 pm until 8 am; or day – from 8 am until 8 pm).

A comparison between survivors and nonsurvivors at hospital discharge was performed.

Statistical analysis

Standard descriptive statistics were used. Continuous variables were reported as median [interquartile range (IQR)] or mean ± standard deviation according to data distribution.

Continuous variables were analyzed using the parametric unpaired Student's t test, the nonparametric Mann–Whitney U test or Kruskal–Wallis H test, according to data distribution. Categorical variables were compared using the χ^2 test.

A Receiver Operator Characteristics (ROC) curve was performed to assess the performance of CRP concentration at ICU discharge in the identification of patients with poor outcome. According to the Youden index, a CRP discharge concentration "alert measurement" was defined. The difference in mortality was assessed with Kaplan–Meyer survival curves using a signed log-rank test. To minimize the effect of censored data in the survival analysis, we considered 90-day survival as a target.

We performed a multivariate, backward stepwise, logistic regression analysis with post-ICU in-hospital mortality as the dependent variable. Variables were introduced in the multivariate model if significantly associated with a higher risk of post-ICU in-hospital mortality on a univariate basis at $p < 0.05$. Multicolinearity between all these discrete variables was checked by computing pairwise correlation coefficient (r) between variables taken two by two. An $r < 0.4$ was considered low enough to exclude correlation between the predictors. The adjusted odds ratio (AOR) and the corresponding 95% confidence interval (CI) for each variable were computed.

Tests were performed two-tailed and considered significant when $p < 0.05$. All statistical tests were performed using SPSS for Windows (version 16.0: SPSS, Chicago, IL, USA).

Results

During the study period, a total of 457 patients were admitted to the ICU. The whole population had a mean SAPS II score of 48.1, a standardized mortality ratio of 43.2% and a mean LOS of 7.5 ± 9.8 days. The ICU mortality was 31.5% resulting in 296 patients discharged alive, which constituted our patient population (Figure 1).

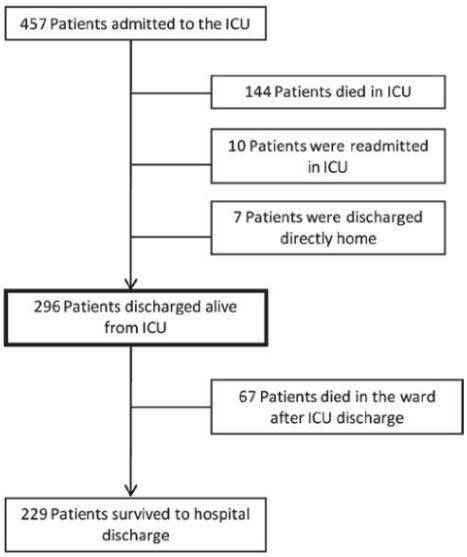

Figure 1. Flow chart showing the number of patients admitted and discharged alive from the ICU during the study period.

Among the patients discharged to the wards/high dependency units, the post-ICU in-hospital mortality rate was 22.6% ($N=67$), corresponding to a cumulative mortality of 46.2%. Half of the deaths in the wards/high-dependency units occurred within 7 days of ICU discharge (median 7 [22] days), and roughly one third in the first 48 h, of which only one after being readmitted to the ICU. Overall the ICU readmission rate was 4.7%.

Clinical and demographic characteristics of the post-ICU in-hospital survivors and nonsurvivors are presented in Table 1.

Nonsurvivors were significantly older, had a longer ICU LOS, had a higher comorbidity score (assessed by Charlson comorbidity score) and higher severity scores. In addition, nonsurvivors had longer duration of mechanical ventilation, of renal replacement therapy and of central venous catheterization. The presence of a tracheostomy at the time of ICU discharge was significantly associated with a higher risk of post-ICU in-hospital mortality (36.4% *vs.* 11.0%, $p<0.001$). No influence of the discharge time (day or night) on the mortality rate was found.

The CRP concentration was higher at the day of ICU discharge in nonsurvivors (7.9 [9.6] mg/dL *vs.* 4.9 [7.6] mg/dL), while haemoglobin was significantly lower (9.6 ± 2.2 g/dL *vs.* 10.5 ± 2.1 g/dL), $p=0.006$ and $p=0.008$, respectively (Table 1).

The area under the ROC curve for CRP concentration at the day of ICU discharge was 0.61 (95%CI, 0.53–0.69). A CRP discharge concentration higher than 6 mg/dL was identified as an "alert measurement", better predicting post-ICU in-hospital mortality, with a sensitivity of 0.67 and a specificity of 0.56.

According to this threshold, "alert measurement", a Kaplan–Mayer survival curve was plotted for patients with a CRP ≥ 6 mg/dL or CRP < 6 mg/dL (Figure 2). A higher mortality was noted in patients with CRP ≥ 6 mg/dL, and that became apparent soon after ICU discharge (log rank = 6.75; $p=0.009$).

A multivariate logistic regression analysis was performed with post-ICU in-hospital mortality as the dependent variable. We included six different variables age, ICU LOS, Charlson comorbidity score, CRP "alert measurement", haemoglobin concentration at ICU discharge and the presence of tracheostomy in this model. The duration of mechanical ventilation, of renal replacement therapy and of central venous catheterization

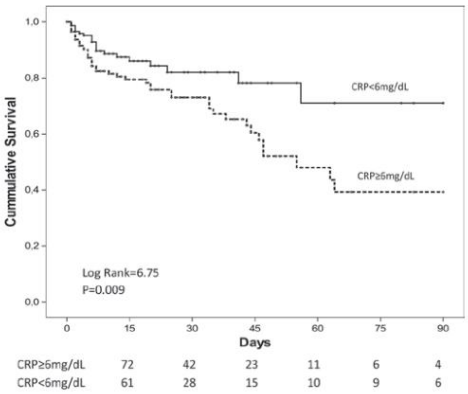

Figure 2. Kaplan–Meyer survival curves according to the presence of the "alert measurement" of CRP concentration (≥6 mg/dL). A significantly higher mortality rate was noted soon after discharge in patients with a CRP concentration of 6 mg/dL or over. Events were censored 90 days after ICU discharge.

Table 1. Comparison of survivors and nonsurvivors characteristics at ICU discharge.

Variable	Survivors ($n=229$)	Nonsurvivors ($n=67$)	p value
Male sex, N (%)	126 (55.0)	32 (47.8)	0.295
Age, years (mean ± SD)	62.4 ± 17.9	72.5 ± 14.4	<0.001
ICU length of stay, days (median [IQR])	4 [6]	7 [10]	0.001
Hospital post-ICU length of stay, days (median [IQR])	14 [22]	7 [22]	0.003
Charlson comorbidity score (mean ± SD)	3.5 ± 2.5	4.8 ± 2.5	<0.001
SAPS II (mean ± SD)	40.9 ± 14.4	53.5 ± 12.5	<0.001
Infection on ICU, N (%)	106 (46.3)	39 (58.2)	0.086
Mechanical ventilation, N (%)	156 (69.6)	54 (80.6)	0.079
Mechanical ventilation, days (median [IQR])	4 [5]	6 [8]	0.007
Renal replacement therapy, N (%)	28 (12.4)	14 (20.9)	0.081
Renal replacement therapy, days (median [IQR])	4 [5]	11 [11]	0.002
Central venous catheterization, days (median [IQR])	6 [6]	8 [11]	0.001
Tracheostomy at discharge, N (%)	25 (11.0)	24 (36.4)	<0.001
Discharge haemoglobin, g/dL (mean ± SD)	10.5 ± 2.1	9.6 ± 2.2	0.008
Discharge platelet count, $\times 10^9$/L (median [IQR])	221 [171]	235 [210]	0.679
Discharge CRP ≥ 6 mg/dL[a], N (%)	102 (44.5)	45 (67.2)	0.001
Discharge during nocturnal period (8 pm–8 am), N (%)	13 (5.7)	3 (4.4)	0.536

SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; CRP, C-reactive Protein.
[a]Refer to text for further details.

Table 2. Summary of multivariate analysis with post-ICU in-hospital mortality as the dependent variable..

Variables	AOR	95% CI	*p* value
Presence of tracheostomy	3.8	1.8–8.3	0.001
CRP "alert measurement"	2.8	1.4–5.7	0.003
Charlson comorbidity score[a]	1.2	1.1-1.4	0.005

Variables excluded from the final model: Age, Intensive Care Unit length of stay and haemoglobin. CRP "alert measurement" was defined as a CRP of ≥ 6 mg/dL. AOR, Adjusted odds ratio; CI, Confidence interval; CRP, C-reactive protein.
[a]Per point.

were excluded because they were found to be collinear with ICU LOS.

The SAPS II score were also injected in the model to assess the effect of patient severity. The variables found to be independently associated with post-ICU in-hospital mortality were the presence of tracheostomy, the Charlson comorbidity score and the CRP "alert measurement" at the day of ICU discharge (Table 2).

Discussion

In the present study, we evaluated the performance of several readily evaluable parameters to assess the risk of post-ICU in-hospital mortality. We identified the presence of tracheostomy, higher Charlson comorbidity score and CRP concentration at ICU discharge to be independently associated with post-ICU in-hospital mortality. In fact, a CRP ≥ 6 mg/dL constituted an "alert measurement" signalling a patient with an increased risk of dying while still in the hospital.

Some studies evaluated distinct risk factors of post-ICU in-hospital mortality, essentially patients' demographic and clinical characteristics.

Several authors (Smith et al., 1999, Daly et al., 2001, Azoulay et al., 2005, Campbell et al., 2008, Sakr et al., 2008) found age to be an independent risk factor for post-ICU in-hospital mortality, whilst in our study, age, although also higher in nonsurvivors, was not independently associated with post-ICU in-hospital mortality. Furthermore, contrary to other studies (Smith et al., 1999, Valentin et al., 2003), male gender was not also associated to higher post-ICU in-hospital mortality.

The patients' previous comorbid condition have a significant impact on ICU mortality (Quach et al., 2009) and may also play a role on predicting post-ICU in-hospital survival (Azoulay et al., 2005, Sakr et al., 2008). In our study, we evaluated comorbidities with the Charlson comorbidity score, which proved to be an independent predictor of post-ICU in-hospital mortality. Also patients with a prolonged ICU LOS have been proposed to have a high risk of post-ICU in-hospital death (Daly et al., 2001, Iapichino et al., 2003). We found the same association in our study, although it was not independently associated with mortality.

The ICU admission severity scores, validated for predicting the risk of in-hospital mortality, had also been studied to assess post-ICU in-hospital mortality. As expected, since post-ICU is still part of in-hospital mortality, we and other authors (Smith et al., 1999, Azoulay et al., 2005, Iapichino et al., 2003) found SAPS II to be associated with post-ICU in-hospital mortality. Consequently in this study both ICU and post-ICU mortality were found to be high, in accordance with the high mean SAPS II score.

The association between length of exposure to invasive devices and post-ICU in-hospital mortality is less well documented. Several studies documented a significantly longer duration of mechanical ventilation in nonsurvivors (Daly et al., 2001, Campbell et al., 2008), similar to our findings. We also found longer periods of renal replacement therapy and central venous catheterization in nonsurvivors. However, the duration of all these procedures were collinear with ICU LOS and therefore not independently associated with post-ICU in-hospital mortality.

The presence of tracheostomy at the time of ICU discharge was independently associated with post-ICU in-hospital mortality, as was shown not only in our study but also by Fernandez et al. (Fernandez et al., 2008). Although tracheostomy may facilitate weaning from mechanical ventilation, ICU discharge and increase ICU survival, some of these patients ultimately die in the wards. Nevertheless, it is not clear whether tracheostomy is a marker of higher illness severity or if it is, by itself, a mortality risk factor. In fact, patients who need a tracheostomy usually have a high burden of neurological or respiratory disease that, by itself, may increase their risk of death.

Night discharge from the ICU was also associated with an increased post-ICU in-hospital mortality, as was shown by Beck et al. (Beck et al., 2002), as well as in a Canadian (Laupland et al., 2008) and in an Australian study (Pilcher et al., 2007). However, we and others (Iapichino et al., 2003, Hanane et al., 2008) were unable to find such an association.

Serum biomarkers associated with increased post-ICU in-hospital mortality would be much useful, especially if easy to measure, simple to interpret and readily available. Several variables have been studied, namely procalcitonin, lactate and CRP (Ho et al., 2008, Castelli et al., 2004, Silvestre et al., 2010). Nevertheless only CRP concentration at the day of ICU discharge had been significantly associated with subsequent post-ICU in-hospital mortality (Ho et al., 2008, Castelli et al., 2004, Litton et al., 2007). In our study an independent association between a CRP concentration "alert measurement" (≥6 mg/dL) and post-ICU mortality was found (AOR of 2.8, 95% CI 1.4–5.7, $p = 0.003$). Therefore, we can speculate that these patients, with CRP concentration at discharge time over this "alert measurement", may potentially benefit from a full workup in order to exclude an ongoing inflammatory or infectious process that may jeopardize their survival probability. A recent study had unveiled a relationship between CRP variation before ICU discharge and mortality. Failure to decrease CRP concentration at least 25% in the last 24 h before ICU discharge was associated with a

significantly higher risk of death (23% vs. 11%, $p=0.002$) (Ranzani et al., 2011).

CRP is an acute phase protein with a good correlation with the inflammatory response (Póvoa, 2008). An elevated CRP concentration at the time of ICU discharge may be a surrogate marker of a persistent inflammatory process, leading to a higher mortality risk.

Although one recent study (Silvestre et al., 2010) did not found this correlation between CRP concentration at the day of ICU discharge and post-ICU in-hospital mortality, it may have been underpowered to unveil such a relationship.

Most of the authors point out the shortage of ICU beds as the reason for early discharge of patients to the ward. The use of these risk factors to stratify patients' post-ICU in-hospital mortality risk may facilitate the selection of those who would benefit from being discharged to high-dependency units or even from being retained in the ICU (Daly et al., 2001).

Our study has some limitations. It was an observational, retrospective study, although using data prospectively collected in the ICU database, encompassed only one centre and was not controlled to withdrawal of life support decisions or neurological status at ICU discharge. Also there was no written discharge policy and those patients clinically perceived as with a high risk may have been treated differently. Nevertheless, it involved a large population, including all patients discharged to the wards/high dependency units, with complete follow-up and evaluated a large number of variables, which strongly support its conclusions.

Conclusion

An "alert measurement" CRP concentration at the day of ICU discharge (≥6 mg/dL), an elevated Charlson comorbidity score and the presence of tracheostomy were independently associated with an increased risk of post-ICU in-hospital mortality. These parameters may be used for risk stratification and decision making, to facilitate the selection of patients who may safely be early discharged from the ICU and to improve outcomes.

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Declaration of interest

The authors declare that they have no conflicts of interest related to this article.

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6.5 Artigo 5: Diagnostic accuracy of C-reactive protein and procalcitonin in the early detection of infection after elective colorectal surgery – a pilot study

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RESEARCH ARTICLE Open Access

Diagnostic accuracy of C-reactive protein and procalcitonin in the early detection of infection after elective colorectal surgery – a pilot study

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Abstract

Background: Colorectal surgery is associated with postoperative infectious complications in up to 40% of cases, but the diagnosis of these complications is frequently misleading, delaying its resolution. Several biomarkers have been shown to be useful in infection diagnosis.

Methods: We conducted a single-centre, prospective, observational study segregating patients submitted to elective colorectal surgery with primary anastomosis, CRP and PCT were measured daily. We compared infected and non-infected patients.

Results: From October 2009 to June 2011, a total of 50 patients were included. Twenty-one patients developed infection. PCT and CRP before surgery were equally low in patients with or without postoperative infectious complications. After surgery, both PCT and CRP increased markedly. CRP time-course from the day of surgery onwards was significantly different in infected and non-infected patients ($P = 0.001$) whereas, PCT time-course was almost parallel in both groups ($P = 0.866$). Multiple comparisons between infected and non-infected patients from 5th to 9th postoperative days (POD) were performed and CRP concentration was significantly different ($P < 0.01$, Bonferroni correction), on the 6th, 7th and 8th POD. A CRP concentration > 5.0 mg/dl at the D6 was predictive of infection with a sensitivity of 85% and a specificity of 62% (positive likelihood ratio 2.2, negative likelihood ratio 0.2).

Conclusions: After a major elective surgical insult both CRP and PCT serum levels increased independently of the presence of infection. Besides serum CRP time-course showed to be useful in the early detection of an infectious complication whereas PCT was unhelpful.

Keywords: C-reactive protein, Procalcitonin, Biomarkers, Colorectal surgery, Surgical infections

Background

Elective colorectal surgery is associated with postoperative infectious complications in up to 40% of the cases [1,2]. Despite recent advances in both surgical technique and perioperative care, infectious complications remain a major clinical problem in colorectal surgery, contributing to significant postoperative morbidity, increased mortality, prolonged hospital stay and additional costs [3-6]. As a result, early diagnosis of the infectious complications is a crucial step in order to initiate treatment as soon as possible [7].

Nonetheless, the diagnosis of infectious complications after elective colorectal surgery is frequently misleading, delaying its resolution. Consequently the availability of an early sensitive and specific marker of postoperative infectious complications would be of great interest [8].

Several biomarkers of infection, namely C-reactive protein (CRP) and procalcitonin (PCT), have been shown to be useful in the diagnosis of infection in different clinical settings as well as in the assessment of its response to antibiotic therapy [9-11].

C-reactive protein has been studied by several authors as an early predictor of abdominal septic complications after esophageal, pancreatic and rectal resection with

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sensitivities and specificities between 65 and 80% [12-15]. Reith et al. used PCT to identify patients with postoperative complications after elective surgery of the colon and the aorta [16]. In this study, on the first postoperative day (POD) serum PCT was higher in patients with complications (6.9 versus 1.12 ng/mL) [16]. However, the preoperatively PCT levels were already higher in the group with complication.

C-reactive protein (CRP) is one of these biomarkers and probably the most widely used. In different infections and clinical settings, the course of relative CRP variations and the CRP ratio, can discriminates, early in the clinical course, survivors from non-survivors [17,18] [19]. The identification of the individual pattern of CRP ratio response to antibiotic therapy appears to be a reflection of the clinical course of infection independently of other possible confounders [20].

Recently Oberhofer and colleagues [21] demonstrated in a prospective study in patients submitted to elective colorectal surgery that CRP concentrations were not inferior to PCT levels in identifying patients with infectious postoperative complications. In this study ROC curve analysis showed that CRP concentrations on POD 3 and PCT concentrations on POD 2 had similar predictive values for the development of infectious complications (AUC 0.746 and 0.750, respectively).

To the best of our knowledge, this is the only study that compared the diagnostic accuracy of CRP and PCT for early detection of postoperative complications in patients undergoing colorectal surgery.

The present study was designed to assess the value of serum CRP and PCT time course in the postoperative setting of elective colorectal surgery with primary anastomosis and its potential in detecting infectious postoperative complications.

Methods

The present study was a prospective, single centre, observational study conducted during a 21 months period, between October 2009 and June 2011, in the General Surgery Department of São Francisco Xavier Hospital. Our hospital is a central and university hospital of Lisbon that belongs to a Hospital of 900 beds. Fifty patients with elective colon resections with primary anastomosis were prospectively included in the present study. Inclusion criteria were age >18 and elective colon resections. Patients were excluded if they were on systemic antibiotics at the time of surgery, if it was not able to obtain an informed consent and if they were in other clinical trial. The West Lisbon Hospital Centre Ethics Committee previously approved the study. Informed consent was obtained from all patients or legal representative before surgery.

Data collection and definitions

Data on patient demographics, surgical procedures, postoperative mortality and morbidity were prospectively collected from medical records. The baseline characteristics of the patients enrolled in the study are detailed in Table 1.

Postoperative infectious complications were defined as follows: anastomotic leakage (AL), abscess, surgical site infection, pneumonia, urinary tract infections and central line infections.

Patients underwent further postoperative diagnostic test or treatment only in case of symptoms or signs of an infectious complication. An AL was verified either by radiography enema performed with computed tomography scan, x-ray or by endoscopy. Abscesses were verified by purulent drainage or during re-laparotomy. Surgical site infection was diagnosed by the presence of clear signs of inflammation at the wound margin or purulent drainage from the wound [22]. Diagnosis of central line infection required positive blood cultures and cultures from the catheter tip with the same microorganism [23]. Pneumonia was diagnosed by the presence of new pulmonary infiltration chest radiography or in chest CT scan accompanied by clinical symptoms of the lower respiratory tract or on physical or laboratory exam [24]. Urinary tract infection was defined by positive urine sediment analysis combined with fever and/or leukocytosis [25].

Pneumonia and UTI were treated with antibiotics; central line infections were treated with antibiotics and removal of the catheter; surgical site infections were treated with drainage and antibiotics; AL and abdominal abscess were treated with re-laparotomy and antibiotics.

Serum CRP, PCT, white cell count (WCC), platelets and higher body temperature were recorded routinely before surgery, and on POD 1 to 12 or before if the patient was discharge earlier.

Biomarkers measurements

Measurement of CRP was performed by an immunoturbidimetric method (Tina-quant CRP; Roche Diagnostics, Mannheim, Germany). The precision of the assay measured by the intra- and inter-assay coefficient of variation was < 7%, the sensitivity of the method was 0.1 mg/dL and the detection limit was 0.3 mg/dL.

Procalcitonin was quantified by sensitive time-resolved amplified cryptate emission assay (Kryptor PCT, B.R.A.H.M.S AG, Hennigsdorf, Germany). The precision of the assay measured by the intra- and inter-assay coefficient of variation was between 2 and 3%, the sensitivity of the method was 0.01 $ng.mL^{-1}$ and the detection limit was 0.06 $ng.mL^{-1}$.

Comparison between infected and non-infected patients after elective colorectal surgery with primary anastomosis was performed.

Table 1 Clinical and demographic characteristics of the patients treated by colorectal resection

	Non-infected N = 29	Infected N = 21	*P*
Age, yrs	70.3 ± 10.9	70.7 ± 7.2	0.873
Male sex (M/F)	18/11	14/7	0.042
Body mass index	26.5 ± 5.0	28.5 ± 6.3	0.176
Charlson score, points	4.45 ± 1.64	3.86 ± 1.42	0.19
Co morbidities, N (%)	26 (89.7)	19 (90.5)	0.924
Diagnosis			0.971
Cancer, N (%)	24 (82.8)	17 (80.9)	
Diverticular disease, N (%)	4 (13.8)	3 (14.3)	
Other, N (%)	1 (3.4)	1 (4.8)	
Location of the disease			0.173
Ascending colon, N (%)	13 (44.8)	5 (23.8)	
Descending colon, N (%)	3 (10.3)	1 (4.8)	
Sigmoid / Rectum, N (%)	13 (44.8)	15 (71.4)	
Bowel preparation, N (%)	19 (65.5)	18 (85.7)	0.191
Antibiotic prophylaxis, N (%)	25 (86.2)	20 (95.2)	0.383
Surgical intervention			0.2
Right hemicolectomy, N (%)	13 (44.8)	4 (19.1)	
Left hemicolectomy, N (%)	3 (10.3)	2 (9.5)	
Sigmoidectomy, N (%)	6 (20.6)	9 (42.9)	
Total colectomy, N (%)	0	1 (4.8)	
Anterior resection, N (%)	7 (24.1)	4 (19.4)	
Other, N (%)	0	1 (4.8)	
Type of infection, N			
Anastomotic leak		1	
Intraabdominal abcess		1	
Surgical site infection		16	
Central line infection		1	
Pneumonia		1	
Urinary tract infection		1	
Infection diagnosis, day		7.2 ± 2.3	
Admission in ICU, N (%)	7 (50)	7 (50)	0.534
Length of stay, days	11 [7]	21 [14]	0.001
Mortality, N (%)	0	2 (9.5)	0.171
Preoperative CRP, mg/dL	0.39 [0.48]	0.5 [2.19]	0.473
Preoperative PCT, ng/dL	0.08 [0.04]	0.08 [0.07]	0.471
Preoperative white cell count, $x10^6$/L	6900 ± 1300	7000 ± 1900	0.891
Preoperative platelets, $x10^9$/L	242 ± 71	259 ± 70	0.389
Preoperative body temperature, °C	36.2 ± 0.4	36.4 ± 0.5	0.221

ICU – Intensive Care Unit; CRP – C-reactive Protein; PCT – Procalcitonin. Data presented as mean ± SD or median [IQR].

Statistics

Results are expressed as the mean ± standard deviation unless stated otherwise. To assess differences between the two main groups, infected and non-infected patients, the Student's t test and the Mann–Whitney U test were used for continuous variables and the $\chi 2$ test was used for categorical variables. Time dependent analysis of different variables was performed with a general linear model, univariate, repeated-measures analysis using a split-plot design approach.

Median values with interquartile range were used for graphical visualization. Logistic regression models were used to determine if each biomarker from the POD5 to POD9 was associated with complications. Bonferroni correction was used to counteract the problem of multiple comparisons [26].

The diagnostic accuracy was evaluated with area under the curve (AUC), using the ROC methodology [27]. The AUCs were computed using the non parametric trapezoidal method and their 95% confidence limits were computed according to method established by DeLong [28].

Results were reported as the odds ratio with a 95% confidence interval. Significance was accepted for $P < 0.05$ unless otherwise stated. Data were analyzed using PASW Statistics v.18.0 (SPSS, Chicago, IL).

Results

Baseline and outcomes

From October 2009 to June 2011, a total of 50 patients were prospectively included.

Infectious complications were diagnosed in 21 patients (42%): sixteen surgical site infections, one AL, one intra-abdominal abscess and three extra-abdominal infections. The median day of diagnosis of complications was POD7 (interquartile range (IQR) 5–12). Infection was less frequent in men (28% vs. 72%, P = 0.042).

Diagnosis, comorbidities and surgical procedures were similar in patients with and without infectious complications.

Of the 50 patients, 14 (28%) were admitted in the Intensive Care Unit and two (4%) patients died due to nosocomial infections. Clinical and demographics characteristics are expressed in Table 1.

White cell count, platelets and body temperature time course

Mean preoperative values of WCC, platelets and body temperature were similar in infected and non-infected patients (Table 1). In the POD1, WCC increased in both groups, being slightly higher in the infected group although not reaching statistical significance (Figure 1C).

Platelets decreased after surgery, reaching the lower value on the POD2 and gradually increased thereafter in both groups (Figure 1D).

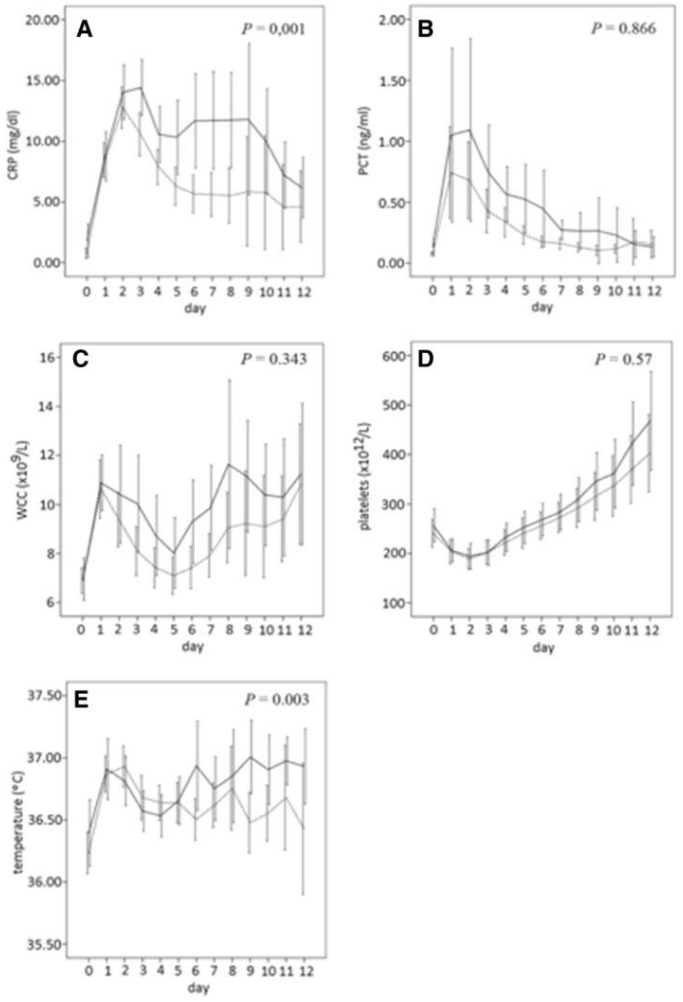

Figure 1 Observed means of C-reactive protein (A), procalcitonin (B), white cell count (C), platelets (D) and temperature (E) during the first 12 days after elective colo-rectal surgery for non-infected (dashed line) and infected (solid line) patients. Error bars represent point-wise 95% confidence intervals.

Body temperature was significantly higher on the POD6 in patients who developed a post-operative infection complication (P = 0.003) (Figure 1E), however the absolute difference between the infected and non-infected group was only 0.3°C. These findings promote the use of biomarkers to help the discrimination between infection and non-infection promoting an earlier focus control, since clinical data are many times insufficiently.

CRP and PCT time course

The levels of CRP and PCT before surgery were very low and similar in patients with an uneventful course as

well as in those that went on to develop an infectious complication (0.1 ± 0.06 vs. 0.07 ± 0.04 ng/ml; 1.81 ± 2.83 vs. 0.72 ± 1.12 mg/dl, respectively). After surgery, in the POD1, both CRP and PCT increased : CRP increased more than 15× and peaked at 48 hrs; PCT increased around 10× the basal level and peaked at 24 to 48 hrs (Figure 1A and B).

The CRP time-course from the day of surgery onwards was significantly different in infected and non-infected patients (P = 0.001). After the postoperative peak at 48 hrs, CRP decreased persistently in patients with an uneventful postoperative course (Figure 1A). In opposition, in those that will develop an infectious complications CRP decreased from during the POD2 and POD3 until reaching a concentration plateau between POD4 to POD9. After resolution of infection complication, CRP decreased again reaching at POD12 values close to those of non-infected patients. The lack of decrease in CRP levels in the post operative period is a predictor of post-operative infections in patients submitted to colorectal surgery. In opposition, the PCT time-course was almost parallel in both groups, infected and non-infected (P = 0.866) (Figure 1B).

To assess the diagnostic performance of each biomarker, we performed multiple comparisons between infected and non-infected patients from the POD5 to POD9. The CRP concentration was significantly different (P < 0.01, after Bonferroni correction), on the POD6, POD7 and POD8. The CRP levels predicted the infection in general one-day earlier, since the mean of postoperative infection occurred on POD7.

The results of the CRP ROC analysis to assess the diagnostic performance of surgical infectious complications are shown on Table 2. As early as the POD6, a CRP concentration >5.0 mg/dl was associated to with occurrence of infectious complications, with a sensitivity of 85% and a specificity of 62% (positive likelihood ratio 2.2, negative likelihood ratio 0.2).

Discussion

The early identification of patients who developed infectious complications is crucial for timely and adequate treatment. Severe sepsis is still a major cause of postoperative morbidity and mortality after major surgery, with an incidence ranging between 9 to 12% and high mortality (42% to 80%) [1,29-32].

Table 2 Receiver operating characteristics curve analysis of C-reactive protein during the postoperative course of patients after colorectal surgery

	AUC (95% CI)
CRP POD 6	0.740 (0.599-0.880)
CRP POD 7	0.730 (0.583-0.878)
CRP POD 8	0.750 (0.591-0.909)

CRP - C-reactive Protein; POD – Postoperative day; AUC – area under curve; CI – confidence intervals.

In our study the rate of infectious complications after elective colonic surgery was high, 42%, however the majority (36%) were surgical site infections. An AL was diagnosed in only one patient. The mortality was 4%, similar to the outcomes described in other studies [33,34].

Septic complications after colorectal resection consist mainly of surgical site infections (up to 40%), pulmonary infections (10%) and urinary infections (5%) [2]. Anastomotic leakage and intraabdominal abcess are the most feared complications and are frequently diagnosed late in the postoperative period since the initial clinical manifestations are very subtle. About 30% of patients admitted to the ICU with intraabdominal infection died, with mortality rates even higher when peritonitis arises as a complication of a previous operative procedure [35,36].

A method for the early identification of patients at risk for pos-operative infection would be of clinical importance, since clinical signs are usually insensitive and do not allow an early diagnosis. Several biochemical tests are used to identify persistent inflammatory activity in postoperative patients, including CRP, PCT and interleukins.

The early identification of patients at risk for postoperative infection would be of clinical importance, since clinical signs are usually insensitive and do not allow an early diagnosis. Several biochemical tests are used to identify persistent inflammatory activity in postoperative patients, including CRP, PCT and interleukins [37-39].

In our study, only CRP demonstrated to be useful in discriminating between infected and non-infected patients. The CRP levels predicted the infection in general on POD 6–7, one-day earlier, than the (median) day of post operative infection diagnosis. PCT and the other inflammatory markers were not useful in discriminating between infected and non-infected patients. Despite body temperature at POD6 was significantly higher in patients who developed a post-operative infection complication the difference between groups was only 0.3°C and no clinical significance was attributable. Recently, in a similar study Oberhofer et al. [21] demonstrated that both CRP and PCT in the early postoperative period, with a significant difference between patients with and without infectious complications.

In our study, PCT failed to discriminate between infected and non-infected patients. Meyer et al. recently reported in literature that in critically ill surgical patients an increase in PCT levels did not help to predict surgical complications [40].

It is well known that after of the presence a major elective surgical insult both CRP and PCT serum levels markedly increased independently of infection. It is

demonstrated that by using a model of systemic inflammation after intravenous endotoxin administration, showed that PCT levels in healthy subjects reached a maximum by 24 h and remained above normal for >7 days. In contrast, CRP had normalized in the same subjects by 7 days [41]. Despite this data clinical studies are controversial Lindberg et al. in a series of 47 patients with major abdominal surgery and a uneventful post-operative course, mean CRP increased in the first 48 hrs and reached half its maximum value on the POD5 whereas PCT declined after 24 hrs [42]. On the other hand Meissner et al. [43] described that peak PCT levels are reached within 24 hours postoperatively and return to normal levels within the first week, depending the degree of PCT elevation on the intraoperative course and the type of the surgical procedure.

In our study the peak of PCT was reached between 24 and 48 hrs, after this period PCT could not discriminate between infected and non-infected patients. In our study after the postoperative peak at 48 hrs, CRP decreased persistently in patients with an uneventful postoperative course and at POD11 CRP was <50% the basal level.

CRP kinetics has been recently described by several authors as a predictive of infectious postoperative complications [15,44]. CRP has been studied in detecting AL after rectal resection. Two recent studies reported that persistently increased CRP values after POD 2–4 were associated to a later diagnosis of an AL [15-45].These authors found that prolonged elevation and/or a absence of decline in CRP levels were associated with more infectious complications and poor outcome [15,44].

More recently Warschkow et al. [46] demonstrated that CRP values exceeding 123 mg/l on POD 4 where associated a higher risk of infectious complications. These authors found that CRP level above 143 mg/L had a good diagnostic accuracy to detect infectious complications with an AUC ROC 0.76 [46]. We found similar results and CRP time course showed to be useful in the early detection of an infectious complication after elective colorectal surgery. The highest diagnostic accuracy was observed for CRP measured on POD 8, with an AUC of 0.75. However, already by POD6, that is to say 1 day before the median day of infectious diagnosis, the CRP AUC was 0.74.

Some authors advocate the use of PCT as an early biomarker of infection. Takakura et al. recently reported in 18 patients with surgical site infections (SSI) in patients undergoing elective colorectal resection that PCT was significantly higher than CRP levels [47]. Nevertheless higher PCT levels were found on POD1 that could be due to the surgical insult. Reith et al. found, in a prospective study involving 70 patients, 35 with intra-abdominal colorectal elective surgery, that PCT levels were closely related to postoperative complications (severe pneumonia, ischemia, and AL) [16]. PCT was measured preoperatively and postoperatively from day 1 to 5 and on days 7 and 10. These authors could not found any differences between groups in other markers of infection such as WCC, CRP, IL-6 and body temperature. However preoperative CRP concentrations in complicated patients were already significantly higher compared to those who do not develop complications, questioning if there was underlying infection prior to surgery. Novotny et al. more recently found in 104 patients with secondary peritonitis that PCT ratio appears to be helpful in distinguishing between patients with successful eradication of the septic focus and those with a persisting infectious focus [48]. In this study CRP was not evaluated [48]. Recently Lagoutte et al. in a study that included patients undergoing elective colorectal surgery could not found differences between PCT and CRP for the detection of AL with a better AUC ROC for CRP on POD 4 [49]. Despite this data were not confirmed by the Garcia-Granero group that demonstrated a PCT superiority in the AL diagnosis [50], both studies only study the AL complication and did not performed a time dependent analysis study.

Our data found that PCT time course could not differentiate between patients who developed complications with lower AUC ROC than those found in CRP.

Few studies have investigated the use of PCT in the diagnosis of intra-abdominal infections. While PCT showed promise as a marker to exclude perforation and ischaemia in obstructive bowel syndrome, the utility in acute appendicitis and pancreatitis was limited [51-54].

In 1993, Assicot et al. showed in children that PCT levels were high in severe bacterial infections in contrast with those who had absent, localized or viral infections [55]. Some authors advocate that patients who have a localised infection without a general systemic response do not appear to have high levels of serum PCT. An extrapolation as been made to patients who do not develop a marked systemic inflammatory response syndrome such as the elderly or the malnourished patient, although this has not been tested [56].

In the present study, most of the infected patients had surgical site infections that could be considered a localised infection and as a result could justify the lack of sensitivity for PCT.

Similar to previous published studies, measurements of WCC contribute little to the early detection of infectious surgical complications [46].

Our pilot study has some limitations. It is a single-centre study and the number of clinical events (21 patients with infection complications) is small which limits the statistical power of our analysis. However, as far as we are aware, this is the first prospective study in elective colorectal surgery that evaluate two biomarkers

simultaneously, CRP and PCT, with measurements before the surgery and a 12 days follow-up.

Recently other biomarkers like lipopolysaccharide-binding protein (LBP) have been study as screening tools for AL and increased concentrations of LBP in drain fluid were associated to a higher chance of AL. However, future studies are needed to validate this biomarkers [57].

Despite these limitations our study provides support to use serial measurements of CRP after elective colorectal surgery for early identification of patients at risk of developing infections, that is to say even before infection diagnosis, having CRP a lower cost of CRP compared to the PCT.

Conclusions

Our study suggested that serial CRP measurements after elective colorectal surgery could be used as a diagnostic biomarker in the early prediction of postoperative infectious complications. A prolonged elevation of CRP levels with no subsequent decrease precedes the detection of infection by one day on average. In the present study serial PCT measurements after elective colorectal surgery were unhelpful in prediction of postoperative infectious complications.

Competing interests

The authors declare that they do not have competing interests in this study.

Authors' contributions

JS participated in the design of the study, performed the statistical analysis and wrote the manuscript. JR and PP conceived of the study, and participated in its design and coordination and helped to draft the manuscript. CL helped in the database and to draft the manuscript. All authors read and approved the final manuscript.

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6.6 Artigo 6: suPAR in the assessment of post-ICU prognosis – a pilot study

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suPAR in the assessment of post-ICU prognosis - a pilot study

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suPAR in the assessment of post-ICU prognosis - pilot study

INTRODUCTION

In-hospital death following intensive care unit (ICU) discharge has been estimated to be 5%–27% and nearly 10% of patients require ICU readmission (1-4). Despite improvements in ICU care quality and widespread utilization of step-down units over the last decades, a significant number of patients still die in the hospital following successful ICU discharge (5), therefore, an adequate evaluation is necessary to detect individuals at high risk of unfavourable outcomes.

Several scores have been developed, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score (6), the mortality probability models (7), the Simplified Acute Physiology Score (SAPS) II (8), and more recently the SAPS3 (9), among others. Almost all severity scores use a group of demographic, clinical and physiological variables from the first day of ICU stay to obtain an individual patient score and a prediction of in-hospital mortality. Usually the above mentioned severity scores are used to monitor the performance of a single ICU, to adjust mortality of different ICUs to its case-mix and for helping in guiding resource allocation (10). The currently available models are not useful and were not designed neither validated for individual patient management (11, 12). These scores were also not designed to evaluate post-ICU discharge prognosis (2, 7, 13-16).

Some authors advocate that the pro- or anti-inflammatory status of the patient could be used as potential risk factor at ICU discharge (17, 18). Biomarkers, such as CRP, procalcitonin (PCT) and lactate, have been studied in hospital and ICU outcome with conflicting results (19-21).

Systemic levels of soluble urokinase-type plasminogen activator receptor (suPAR), a protein derived from cleavage and release from neutrophils, lymphocytes, endothelial and malignant cells has recently been recognize as a potential prognostic biomarker of infectious disease (22). Various studies have been conducted with suPAR. The majority of these studies have focused on the ability of suPAR to predict sepsis and mortality in patients with bacteremia, systemic inflammatory response syndrome, sepsis, and septic shock (23-26). Systemic levels of suPAR have been found to be significantly higher in

critically ill patients with poor outcome (27). The role of suPAR as a prognostic marker of hospital mortality after ICU discharge has not been evaluated. Systemic levels of suPAR remain elevated long after clinical recovery and only decline after several weeks (28). Therefore, the use of suPAR seems to be a promising prognostic marker in critically ill patients.

The aim of our study was to determine the predictive value of suPAR in the assessment of outcome (hospital mortality) of patients discharged alive from ICU.

METHODS

We conducted a prospective, single centre, observational study during a 24-month period (June 2011-June 2013) at the ICU of São Francisco Xavier Hospital, an 8-bed multidisciplinary ICU.

The local Ethics Committee approved the study design. Informed consent was obtained from all patients or legal representative before study inclusion.

All patients discharged alive from the ICU were included, except those with age < 18 years, those transferred to another ICU, and the ones with a do not resuscitate status.

Patients were followed until hospital death or hospital discharge.

Patient's survival at 28 and 90 days after ICU discharge were also analysed.

Data collected included: admission diagnosis and past medical history; vital signs were evaluated hourly and daily extreme values were recorded; Acute Physiology and Chronic Health Evaluation II (APACHE II) was calculated at 24 h of ICU admission.

C-reactive protein levels and white cell count (WCC) were measured at admission and daily until discharge; suPAR levels and SOFA score were collected at ICU discharge.

Measurement of CRP was performed by an immunoturbidimetric method (Tina-quant CRP; Roche Diagnostics, Mannheim, Germany).

The suPAR was measured with a venous blood sample collected into an EDTA tube, centrifuged and frozen at -80°C. Measurement were done in duplicate by an enzyme-linked immunosorbent assay (suPARnosticTM, ViroGates, Lyngby, Denmark) following the manufacturer's instructions; the lower limit of detection was 1.1 ng/ml.

A subgroup analysis was performed in patients with sepsis diagnoses. Sepsis was defined according to 2001 international consensus definitions (29).

Statistical analysis

Data was presented as the mean ± standard deviation (SD). Categorical variables were presented as rates or percentages. Comparisons of parametric variables between groups were performed with an unpaired Student's t-test, non-parametric variables were compared between groups using a Mann-Whitney test.

To compare the predictive value of the biomarkers and severity scores, receiver-operating characteristic (ROC) curves were built and the area under the curve (AUC) was determined. DeLong was applied to determinate the statistical significance of the difference between the areas under.

The primary outcome variable was post-ICU mortality.

To study the effect of biomarkers and SOFA on mortality we used logistic regression. The unadjusted odds ratio (OR) and the corresponding 95% confidence interval (CI) for each variable were computed.

The level of statistical significance was set at 0.05 and all tests were two-tailed. We used the SPSS statistical software package 19.0 (SPSS, Inc., Chicago, IL, USA) for all statistical analyses.

RESULTS

Study population

A total of 202 patients (112 women and 90 men) were included, with a mean age of 65.3±16.3 years and APACHE II score of 22,0±9,0. Post ICU hospital mortality rate was 14,6%. The hospital readmissions rate was 38,4%.

Non-survivors were older and more seriously ill, with higher severity scores and requiring more vasopressors. We could not find significant differences in admission diagnosis between groups. Clinical and demographic characteristics are presented in Table 1.

At ICU discharge, non-survivors were also sicker, had higher SOFA ($p < 0.001$) and presented higher suPAR levels ($p=0.003$). The other biomarkers (C-reactive protein and WCC levels) were similar between groups (Table 2).

Prognostic value of the studied variables

Among the studied prognostic variables, the best predictors of post ICU mortality were APACHE II (AUC 0.70) and SOFA (AUC 0.78). The ROC curve for suPAR yielded an AUC of 0.68 ($p=0.002$) higher than the AUC of CRP (AUC 0.54) and WCC (AUC 0.48).

The combination of suPAR with APACHE and SOFA increased the predictive ability (Table 3). Despite the improvement in mortality prediction, it did not reach a combined sensitivity and specificity above 80%.

A multivariate logistic regression analysis was performed with post-ICU in-hospital mortality as the dependent variable. We included five different variables APACHE II and SOFA and biomarkers CRP, suPAR and WCC in this model (Table 4). SOFA was independently associated with a higher risk of hospital mortality (OR 1.673; 95% CI 1.252-2.234), 28 days mortality (OR1.861; 95% CI 1.856-2.555) and 90 days mortality (OR 1.584; 95% CI 1.241-2.022).

Influence of Sepsis

Documented sepsis was present in 101 patients (50%). The presence of sepsis did not influence post ICU outcome, with similar mortality rates between septic and non-septic patients. Similar to general population only SOFA score was associated to poor outcome with a higher risk of hospital mortality (OR 1.876; 95% CI 1.238-2.842) (Table 5).

DISCUSSION

In this prospective observational study we evaluated the performance of suPAR at ICU discharge to predict post-ICU mortality. Our data showed that suPAR levels at ICU discharge were higher in hospital non-survivors.

Besides its accuracy in assessing the risk of post ICU mortality being lower than current severity scores, and its combination with these scores only slightly improved the ability to predict post ICU mortality.

Some authors advocate that post-ICU death could be related to the persistent inflammatory response, with endothelial dysfunction and microcirculatory abnormalities present in non-survivors with higher biomarkers levels (30).

Various biomarkers have been proposed as being of potential use in prognostication; CRP concentrations have been extensively used and correlate with on going organ dysfunction, ICU mortality and probably to the bacterial burden (31-33). This marker is routinely measured at ICU and has advantages of simplicity, reproducibility and speed (31, 34).

C-reactive protein has been studied as a prognostic biomarker in-hospital mortality and readmission after ICU discharge (17, 18, 20). Because these results are seemingly conflicting, there is no evident point of view about the ability to use serum CRP and other biomarkers as a marker of post-ICU prognosis (19, 20, 30).

Recently higher suPAR and proadrenomedullin (proADM) levels at ICU admission seemed to be correlated to hospital mortality in septic patients (35). Similar to our data, in this study, prognostic accuracy was significantly better for severity scores than for any of the analysed biomarkers. The best AUC for the prediction of in-hospital mortality was with APACHE II (0.82) and SOFA (0.75) scores. The ROC curve for suPAR yielded an AUC of 0.67, higher than proADM (0.62), CRP (0.50) and PCT (0.44). The combination of severity scores and each biomarker did not provide better AUCs.

More recently, Jalkanen et al studied a cohort of critically ill non-surgical patients and found that low suPAR concentrations were predictive of survival (36). However in this

study neither classical biomarkers neither severity scores were compared in assessment of risk mortality.

Our study analysed suPAR levels at ICU discharge. The biological characteristics of suPAR, which is only slightly influenced by circadian changes and remains stable in the systemic circulation within the first days of the sepsis course, might explain its superiority over other biomarkers, namely CRP and PCT (27).

However, in our study, suPAR levels, despite being higher in hospital non-survivors, could not be associated with higher risk of death, either alone or combined with the severity scores. In addition, suPAR levels did not show any correlation with post-ICU mortality in septic patients.

We found that a single determination of suPAR on ICU discharge was a better tool in predicting in-hospital mortality than CRP. However, the prognostic accuracy was significantly better for APACHE II or SOFA scores than for any of the analysed biomarkers. The combination of biomarkers with these severity scores only slightly improved their prognostic accuracy. Like other biomarkers, suPAR as a single biomarker is not strong enough of a predictor for clinical decision-making.

CONCLUSIONS

In the present study, we compared severity scoring systems and biomarkers in predicting mortality in patients discharged alive from ICU. Despite suPAR levels are slightly better than common biomarkers, including CRP, they did not present a better performance than severity scores. At ICU discharge suPAR was a poor predictor of post-ICU prognosis.

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Revista Brasileira de Terapia Intensiva

Decision Letter (RBTI-2018-0026.R2)

From: rbti.artigos@amib.org.br
To: joanapsilvestre@gmail.com
CC:
Subject: Revista Brasileira de Terapia Intensiva - Decision on Manuscript ID RBTI-2018-0026.R2
Body: 04-Jul-2018

Dear Dr. Silvestre:

It is a pleasure to accept your manuscript entitled "suPAR in the assessment of post-ICU prognosis - a pilot study" in its current form for publication in the Revista Brasileira de Terapia Intensiva. The comments of the reviewer(s)/associate editor who reviewed your manuscript are included at the foot of this letter.

Your manuscript will now undergo technical and scientific revision. During this process, usually some minor issues are raised. They must be solved before the manuscript is considered ready for publication. Our editorial team will contact you soon. We thank you for your promptness in solving all issues.

Thank you for your fine contribution. On behalf of the Editors of the Revista Brasileira de Terapia Intensiva, we look forward to your continued contributions to the Journal.

Sincerely,
Dr. Thiago Costa Lisboa
Editor-in-Chief, Revista Brasileira de Terapia Intensiva
tlisboa@hotmail.com

Associate Editor Comments to Author:

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7 Considerações finais

Nesta tese foi abordado o prognóstico do doente critico, nomeadamente, o papel dos biomarcadores no *outcome* na data de alta da UCI e na alta hospitalar.

Constituindo a infeção e a sépsis um problema grave, nomeadamente no doente crítico, e dada a elevada morbilidade e mortalidade associadas, (56, 57), foi também avaliado se os biomarcadores poderiam ajudar a definir o prognóstico dos doentes com sépsis.

Têm sido estudadas diversas escalas de gravidade numa tentativa estratificar o doente critico, no entanto, estas têm demonstrado vários problemas. O uso de variáveis fisiológicas em sistemas de pontuação pode originar potenciais vieses e levar ao cálculo impreciso do *score* de gravidade. Os valores das variáveis incluídas podem alterar-se espontaneamente ou como resultado de uma intervenção antes da admissão do doente na UCI tornando o sistema de pontuação impreciso, sugerindo uma menor gravidade com uma menor mortalidade atribuída. No entanto, a sua limitação mais importante é a interpretação inadequada. Temos de estar cientes de que a probabilidade de mortalidade intra-hospitalar com base num determinado índice de gravidade está relacionada a um grupo semelhante de doentes e não com aquele indivíduo em particular, uma vez que estes scores foram desenhados para comparar grupos de doentes de diferentes unidades. Isso é importante para entender antes de tentar usar sistemas de pontuação na prática clínica. Consequentemente, os sistemas de pontuação não devem ser usados para fazer previsões para casos individuais (4, 58).

Os biomarcadores, com base no conceito de inflamação/insulto latente após a doença grave poderiam ajudar a avaliar a gravidade do quadro clínico e o prognóstico, identificando os doentes em maior risco (6).

Globalmente, os resultados dos trabalhos desta tese mostram que a utilização destes biomarcadores como marcadores de prognóstico quer isoladamente quer em conjunto com a restante avaliação clínica e laboratorial não demonstraram serem úteis, quer nos doentes com infeção documentada quer nos doentes sem infeção. Estes

biomarcadores foram avaliados quer no momento da admissão, no insulto inicial, quer após a estabilização e resolução da doença crítica, não havendo impacto na melhoria do prognóstico destes doentes.

A estratificação de gravidade do doente crítico continua a ser uma decisão baseada em dados clínicos, não podendo os biomarcadores substituir o juízo clinico.

A importância do conhecimento da biologia dos biomarcadores é bem documentada nos doentes com falência hepática grave e sépsis. Neste grupo de doentes, é demonstrada a falibilidade da PCR como biomarcador de infeção, podendo a ausência da sua elevação ser útil para definir a gravidade.

Em termos de decisão clínica, a ausência de elevação de PCR num doente com forte suspeição clínica de infeção/sépsis deve constituir um alerta para o despiste de insuficiência hepática grave, utilizando outros meios complementares, nomeadamente o factor V. Por outro lado, a ausência de elevação da PCR num doente que clinicamente tem uma infeção constitui também um sinal de gravidade/suspeita de insuficiência hepática grave associada.

Cada vez mais o exercício da medicina intensiva é efetuado fora das paredes das UCI, apostando-se em sistemas de prevenção da doença crítica ou, pelo menos de deteção precoce evitando a sua progressão, minimizando consumo de camas intensivas e reduzindo a duração de internamento na UCI, e consequentemente, custos de tratamento.

Neste sentido, de forma a complementar o comportamento dos biomarcadores na identificação de infeção documentada, foi efetuado um estudo prospectivo envolvendo doentes de cirurgia eletiva, avaliando os biomarcadores e sua cinética na distinção de doentes que desenvolveram complicações infeciosas pós cirúrgicas. Em relação ao seu papel como marcadores de infeção nos doentes submetidos a cirurgia eletiva, aqui o papel dos biomarcadores, em particular da PCR, parece ser um bom adjuvante como marcador de infeção. Deste modo poder-se-à especular que a utilização seriada deste biomarcador poderá identificar precocemente as complicações infeciosas, facilitando a intervenção precoce nas complicações, melhorando o prognóstico.

A utilização diária da PCR, um biomarcador barato e facilmente acessível, nos doentes operados de alto risco pode ajudar a detectar precocemente as infeções pós-cirúrgicas, evitando deste modo a sua evolução para situações de maior gravidade.

8 Perspectivas para futuras áreas de investigação

8.1 Distinção entre complicações pós-cirúrgicas infeciosas e não infeciosas na cirurgia cardíaca

As complicações infeciosas após a cirurgia cardíaca são relativamente comuns com taxas que variam entre os 5- 21%, aumentando a mortalidade de forma significativa a estes doentes (59-61). Nas cirurgias com circulação extracorporal, o contacto do sangue com uma superfície artificial, assim como as lesões de isquemia e reperfusão dos órgãos alvo, levam a uma libertação de mediadores inflamatórios, que em tudo se assemelha ao síndrome de resposta inflamatório da sépsis. A avaliação seriada dos biomarcadores e da sua cinética poderá ajudar no diagnóstico mais precoce de infeção, consequentemente diminuindo quer a mortalidade quer o consumo de antibióticos.

8.2 Deteção de complicações infeciosas após cirurgia citorredutora com quimioterapia intraperitoneal hipertérmica

As complicações infeciosas após a cirurgia oncológica têm um impacto significativo na mortalidade dos doente, atrasando o tratamento oncológico e com isto diminuindo o tempo livre de doença. Os marcadores inflamatórios têm sido estudados no diagnóstico de infeção nos doentes oncológicos, mas o seu comportamento é desconhecido nos doente submetidos a cirurgia citorredutora com quimioterapia intraperitoneal hipertérmica. Este procedimento leva a uma libertação de mediadores provocando um a síndrome da resposta inflamatória sistêmica. A avaliação seriada e a análise da cinética dos biomarcadores quer séricos quer intraperitoneais poderia ajudar a detectar diferentes padrões evolutivos que ajudem a diferenciar a infeção do SIRS.

Um trabalho de investigação a realizar seria a avaliação sérica diária de biomarcadores clínicos (nomeadamente a PCR, PCT, plaquetas, leucócitos), assim como o doseamento destes biomarcadores no liquido intraperitoneal, e avaliar a sua cinética, verificando se existe algum padrão evolutivo diferente entre os doentes que têm complicações infeciosas pós-operatórias dos que não desenvolvem.

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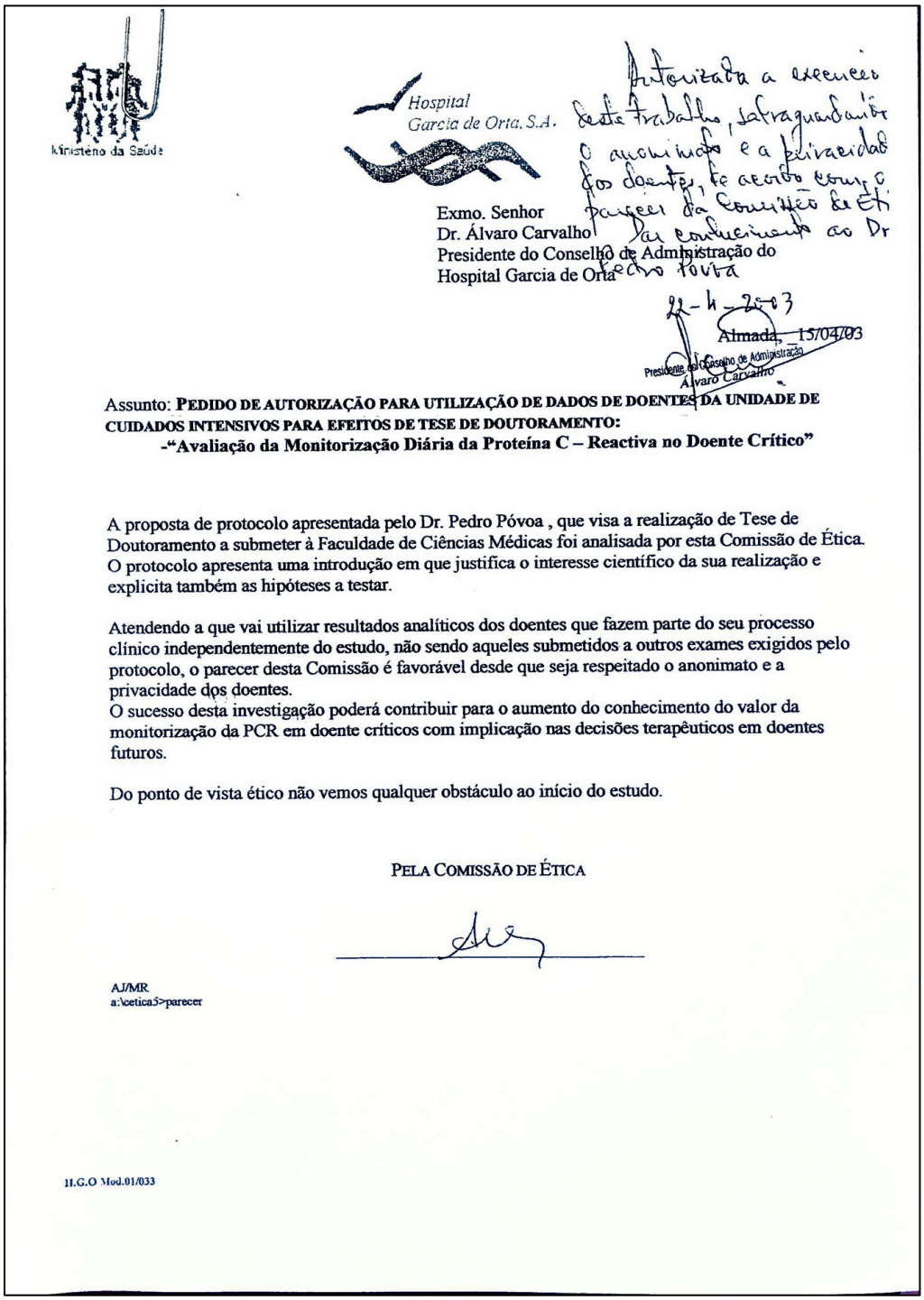
10 Anexos

Em anexo seguem-se os pareceres das comissões de ética relativamente aos dados usadas nos artigos que fundamentam esta tese



Ministério da Saúde

Hospital Garcia de Orta, S.A.

Autorizada a execução deste trabalho, salvaguardando o anonimato e a privacidade dos doentes, de acordo com o parecer da Comissão de Ética. Dar conhecimento ao Dr Pedro Póvoa

22-4-2003

Almada, 15/04/03

Presidente do Conselho de Administração
Álvaro Carvalho

Exmo. Senhor
Dr. Álvaro Carvalho
Presidente do Conselho de Administração do
Hospital Garcia de Orta

Assunto: **PEDIDO DE AUTORIZAÇÃO PARA UTILIZAÇÃO DE DADOS DE DOENTES DA UNIDADE DE CUIDADOS INTENSIVOS PARA EFEITOS DE TESE DE DOUTORAMENTO:**
-"Avaliação da Monitorização Diária da Proteína C – Reactiva no Doente Crítico"

A proposta de protocolo apresentada pelo Dr. Pedro Póvoa , que visa a realização de Tese de Doutoramento a submeter à Faculdade de Ciências Médicas foi analisada por esta Comissão de Ética.
O protocolo apresenta uma introdução em que justifica o interesse científico da sua realização e explicita também as hipóteses a testar.

Atendendo a que vai utilizar resultados analíticos dos doentes que fazem parte do seu processo clínico independentemente do estudo, não sendo aqueles submetidos a outros exames exigidos pelo protocolo, o parecer desta Comissão é favorável desde que seja respeitado o anonimato e a privacidade dos doentes.
O sucesso desta investigação poderá contribuir para o aumento do conhecimento do valor da monitorização da PCR em doente críticos com implicação nas decisões terapêuticos em doentes futuros.

Do ponto de vista ético não vemos qualquer obstáculo ao início do estudo.

PELA COMISSÃO DE ÉTICA

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II.G.O Mod.01/033

Ministério da Saúde

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.

Comissão de Ética

Exma. Senhora,
Dra. Inês Araújo
Serviço de Medicina III
Hospital de São Francisco Xavier
Centro Hospitalar de Lisboa Ocidental, E.P.E.

N.º Referência	Data	N.º Páginas	N.º Anexos
50 / CE - 2011	22-03-2011	1	1

Assunto: *Estudo Observacional* ***"Assessment of risk factors for in-hospital mortality after Intensive Care Unit discharge"***

Exma. Senhora,

Após reunião de 21 de Março de 2011, e estando o estudo de acordo com as normas de submissão impostas pela CE, informo que, em anexo segue o *parecer favorável.*

Com os melhores cumprimentos,

Presidente da Comissão de Ética

Prof.ª Doutora Teresa Marques

MARIA TERESA MARQUES
Presidente da Comissão de Ética

Hospital de Egas Moniz
Rua da Junqueira, 126 / 1349 - 019 Lisboa // Telefone: +351 213 650 000

Ministério da Saúde

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.

Hospital de Egas Moniz

PARECER DA COMISSÃO DE ÉTICA

Estudo Observacional, Título

"Assessment of risk factors for in-hospital mortality after Intensive Care Unit discharge"

Após reunião de 21 de Março de 2011 e, estando o estudo de acordo com as normas de submissão impostas por esta CE, deliberou-se emitir ***parecer favorável*** sobre a realização do mesmo.

A Comissão de Ética solicita ao Investigador Principal que, quando da conclusão deste estudo/projecto, lhe seja enviada uma síntese dos resultados e conclusões do mesmo.

Ouvido o Relator, o processo foi votado pelos Membros da Comissão de Ética do Centro Hospitalar de Lisboa Ocidental presentes em reunião de 21 de Março de 2011:

Presidente: Prof.ª Doutora Teresa Marques

Dr. Carlos Costa, Padre João Valente, Enf.ª Clara Carvalho, Dr. José Santana Carlos, Dr.ª Paula Peixe, Dr.ª Helena Farinha, Dr. Rui Teles

Pelo exposto, emitiu-se a 22 de Março de 2011, **parecer favorável**.

Presidente da Comissão de Ética

Prof.ª Doutora Teresa Marques

MARIA TERESA MARQUES
Presidente da Comissão de Ética

Hospital de Egas Moniz
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REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.

Exma. Senhora,
Dra. Joana Silvestre
Discente de Doutoramento e Assistente Convidada
Faculdade de Ciências Médicas | NOVA Medical School
CEDOC – Universidade Nova de Lisboa

Assistente Hospitalar Graduada de Medicina Interna | Intensiva
Unidade de Cuidados Intensivos Polivalente
Hospital de São Francisco Xavier
Centro Hospitalar de Lisboa Ocidental, E.P.E.

Nossa referência	Data	Nº Páginas
242/CES – 2018	24-09-2018	1

Exma. Senhora,

No seguimento do seu pedido, pede-me a Senhora Presidente desta CES que reencaminhe a declaração sobre o estudo "Identificação precoce de infecções no pós-operatório de cirurgia cólon-rectal electiva com monitorização de PCR e procalcitonina", que obteve parecer da CES em março de 2009 e que segue em anexo.

Com os melhores cumprimentos,

Presidente da Comissão de Ética para a Saúde

Prof.ª Doutora Maria Teresa Marques

MARIA TERESA MARQUES
Presidente da Comissão
de Ética para a Saúde

CES

Comissão de Ética para a Saúde (CES) do CHLO
Hospital de Egas Moniz | Rua da Junqueira, 126 - 1349-019 Lisboa
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REPÚBLICA PORTUGUESA SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.

DECLARAÇÃO

A pedido da interessada, Dra. Joana Silvestre, confirma-se que deu entrada na Comissão de Ética para a Saúde (CES) do Centro Hospitalar de Lisboa Ocidental (CHLO) o estudo intitulado "**Identificação precoce de infecções no pós-operatório de cirurgia cólon-rectal electiva com monitorização de PCR e procalcitonina**", tendo como Investigador Principal o **Dr. Jorge Rebanda**, do Serviço de Cirurgia I do CHLO.

Em reunião de 02 de março de 2009, esta Comissão emitiu parecer favorável à realização do estudo, condicionado à atribuição aos doentes de um número de identificação, escolhido de forma aleatória (de forma a garantir a anonimização).

Lisboa, 24 de setembro de 2018

Presidente da Comissão de Ética para a Saúde

Prof.ª Doutora Maria Teresa Marques

MARIA TERESA MARQUES
Presidente da Comissão
de Ética para a Saúde

CES

Comissão de Ética para a Saúde (CES) do CHLO
Hospital de Egas Moniz | Rua da Junqueira, 126 - 1349-019 Lisboa
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Ministério da Saúde

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.

Comissão de Ética

Exmos. Senhores,
Dra. Joana Silvestre
e
Prof. Doutor Pedro Póvoa
Unidade de Cuidados Intensivos Polivalentes
Hospital de São Francisco Xavier
Centro Hospitalar de Lisboa Ocidental, E.P.E.

N/ Referência	Data	Nº Páginas	Anexos
274/CE -2010	30-11-2010	1	1

Assunto: Projecto ***"Assessment of the prognostic value of soluble urokinase Plasminogen Activating Receptor (suPAR) at ICU discharge – prospective observational study"***

Exmos. Senhores,

Após reunião de 22 de Novembro de 2010, e estando o projecto de acordo com as normas de submissão impostas pela CE, informo que, em anexo segue o ***parecer favorável.***

Com os melhores cumprimentos,

Presidente da Comissão de Ética

Prof.ª Doutora Maria Teresa Marques

MARIA TERESA MARQUES
Presidente da Comissão de Ética

Hospital de Egas Moniz Rua da Junqueira, 126 - 1349-019 Lisboa // Telefone: +351 213 650 000

Ministério da Saúde

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.
Hospital de Egas Moniz

PARECER DA COMISSÃO DE ÉTICA

Projecto, Título

"Assessment of the prognostic value of soluble urokinase Plasminogen Activating Receptor (suPAR) at ICU discharge - prospective observational study"

Descrição:

Em reunião de 22 de Novembro de 2010 e, após recepção do Modelo de Consentimento Informado, estando o projecto de acordo com as normas de submissão impostas por esta CE, deliberou-se emitir ***parecer favorável*** sobre a realização do mesmo.

Ouvido o Relator, o processo foi votado pelos Membros da Comissão de Ética do Centro Hospitalar de Lisboa Ocidental presentes em reunião de 22 de Novembro de 2010:

Presidente: Prof.ª Doutora Teresa Marques

Dr. Carlos Costa, Enf.ª Clara Carvalho, Dr. José Santana Carlos, Dr.ª Paula Peixe, Dr.ª Helena Farinha, Dr. Rui Teles

Pelo exposto, emitiu-se a 30 de Novembro de 2010, **parecer favorável**.

Presidente da Comissão de Ética

Prof. Doutora Teresa Marques

MARIA TERESA MARQUES
Presidente da Comissão de Ética

Hospital de Egas Moniz Rua da Junqueira, 126 - 1349-019 Lisboa // Telefone: +351 213 650 000